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Geneva, 10–15 December 1990

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1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 10 to 15 December 1990. The meeting was opened on behalf of the Director-General by Dr Hu Ching-Li, Assistant Director-General, who informed those present that WHO's revised drug strategy – which devolved from the Conference of Experts on the Rational Use of Drugs convened in Nairobi in 1985 – fully acknowledged the important role of the Expert Committee. He emphasized that the strategy was entirely consonant with the established philosophy of the Expert Committee in that it advocated a comprehensive approach to quality assurance, which, while retaining adequate rigour, had to be adaptable to the needs and economic circumstances of developing countries.

Pivotal to this approach was the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, which provided a simple administrative procedure that enabled importing countries to obtain information on the registration status of a product in its country of origin and to obtain a declaration that the manufacturing facility had been inspected and was operating in compliance with WHO's requirements for good manufacturing practices (GMP). The Certification Scheme had been initially promulgated in 1969 and revised in 1975, and now had the endorsement of 132 participating countries. In 1988 it had been amended to bring within its ambit not only finished dosage forms but drug substances and products of public health relevance intended for veterinary use. Provision had also been made to include complete product information as approved in the country of origin, together with its date of approval.

Dr Hu stressed the importance of giving substance and credibility to the Certification Scheme and to other aspects of quality assurance, especially since the World Health Assembly had in 1988 requested the Director-General "to initiate programmes for the prevention and detection of the export, import and smuggling of falsely labelled, spurious, counterfeited or substandard pharmaceutical preparations". It was for this reason that the Expert Committee was being asked to give priority in the agenda of the present meeting to a consideration of guidelines for the use of the Certification Scheme and of several associated matters, including revised requirements for good manufacturing practices and guidelines for the procedures to be followed in pharmaceutical inspection.

It was evident, none the less, that the certification of imported products and the harmonization of control procedures – important as they were – did not, of themselves, provide a complete assurance of quality. Adequate facilities and technically competent staff to undertake pharmacopoeial analyses remained indispensable. Members were assured that, in maintaining *The international pharmacopoeia* as a compendium of standards founded on classical methods of analysis, the Expert Committee remained strongly identified with the needs of developing countries.

2. Good practices in the manufacture of pharmaceutical products

Several national and regional drug regulatory authorities have already issued guidelines that reflect the ongoing elaboration of the concept of GMP. It is important that these developments be reflected in WHO's requirements for good manufacturing practices, the original text of which was adopted by the Twenty-eighth World Health Assembly in 1975 in resolution WHA28.65 under the title "Good practices in the manufacture and quality control of drugs". The GMP text provides the technical basis for the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (henceforth referred to in this report as the Certification Scheme). Unless the text is revised to reflect advances in pharmaceutical manufacturing technology, including developments in biotechnology, the Certification Scheme will cease to retain global relevance.

The Committee reviewed the proposed revision of the GMP text in the light of comments received from interested parties. It considered that the material could be presented in a more logical sequence if the format of the document were changed, and the definitive document, as subsequently approved by the members of the Committee, is set out in Annex 1, under the new title "Good manufacturing practices for pharmaceutical products".

3. Guidelines on inspection of pharmaceutical manufacturers

The Committee accepted in principle a proposal from the Secretariat that guidelines be developed for official inspections of drug manufacturing facilities to assess compliance with GMP requirements. It acknowledged that these would be of value, particularly to authorities in countries that had only recently engaged in the formulation of finished dosage forms, and that they would strengthen and facilitate the implementation of the WHO Certification Scheme.

The Committee invited comments from governments on the provisional guidelines set out in Annex 2 and recommended that the definitive guidelines be published.

4. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

The Committee considered and provisionally endorsed guidelines for implementing the expanded Certification Scheme (as described in its

thirty-first report (*1*)), together with a set of revised forms proposed for use in the certification process (Annex 3).[1]

In general terms, the objective of the revision is to provide a procedure that is applicable to all circumstances of trade and that ensures more rigorous control through a more effective exchange of information. Three different forms of attestation are proposed:

- a product certificate issued by the competent authority in the exporting country, which should be requested by the importing authority primarily when it intends to issue or vary a product licence;
- a statement of licensing status, also issued by the competent authority in the exporting country, which may be requested by an importing agent who simply needs confirmation whether or not specified products are licensed in the country of origin – information that is important when screening bids made in response to an international tender;
- a batch certificate, which is usually issued by the manufacturer as a warranty that a specific consignment of a product conforms to the documented specification.

The Committee considered that the objectives of the Certification Scheme would be advanced if the three forms, once adopted in their definitive form, were used without further adjustment by all countries participating in the Scheme.

The Secretariat informed the Committee that it expected to be able to present proposals during the Committee's next meeting in 1992 on the certification of active ingredients. As yet, such advice would be premature both because approaches to the necessary administrative controls were still under consideration in many countries and because the control of active ingredients, as opposed to finished dosage forms, would be influenced by some of the proposed revisions of the GMP text.

Because more countries are becoming actively engaged in one capacity or another in new drug development, the Committee agreed that consideration should be given to linking the certification procedure not only to GMP but to other basic norms that need to be observed in drug development work, including good laboratory practice and good clinical practice. It commended the Secretariat for submitting draft criteria defining these concepts to wide consultation.

[1] In May 1992, the World Health Assembly reviewed the proposed guidelines and adopted a resolution (WHA45.29) endorsing "the guidelines for implementation of the WHO Certification Scheme, which will be evaluated and revised, as necessary, in consultation with the Committee on Drug Policies of the Executive Board" and urging Member States "to implement these guidelines, and to issue certificates within five years in a form to be agreed in the light of experience gained in preliminary field testing."

5. Quality assurance of pharmaceutical and biological products manufactured by recombinant DNA technology

The Committee endorsed draft guidelines for assuring the quality of medicinal products prepared by recombinant DNA technology (Annex 4), which had also been considered by the WHO Expert Committee on Biological Standardization (*2*). The document emphasizes, *inter alia*, that the reference preparations needed to permit satisfactory characterization of recombinant products should, whenever possible, themselves be products of recombinant DNA technology. In some cases, it is acknowleged, additional reference preparations are necessary to permit comparison with the naturally occurring substances. The Committee welcomed an offer from the WHO Collaborating Centre for Chemical Reference Substances, Stockholm, Sweden, to collaborate with the National Institute for Biological Standards and Control, England, in the preparation of the required materials.

6. *The international pharmacopoeia* and related activities

6.1 Quality specifications for drug substances and dosage forms

Now that monographs have been prepared and published for virtually all pharmaceutical substances contained in the latest revision of the Model List of Essential Drugs (*3*), work on *The international pharmacopoeia* is currently directed primarily to specifications for dosage forms. The Committee considered and recommended for publication a monograph for topical semi-solid dosage forms, and it acknowledged the progress made in establishing monographs for ophthalmic preparations, suppositories, and the sterility testing of non-injectable preparations. It agreed that a new disintegration test for suppositories should be further examined and that collaborative studies should be undertaken to compare the results obtained by this method with those obtained by established techniques.

6.2 Validation of analytical procedures

Analytical procedures used to control the quality of pharmaceutical substances and dosage forms must be adequately validated. The Committee, in endorsing guidelines submitted by the Secretariat (Annex 5), emphasized that the extent to which validation is necessary is determined by the purpose of the analysis. Judgement on the extent to which the guidelines need to be applied must consequently be made on a case-by-case basis. Currently, the guidelines are directed primarily to the examination of chemical and physicochemical attributes, but many of the general principles are also applicable to microbiological and biological procedures.

6.3 Simple test methodology

Given current concerns in some countries about the inadmissible prevalence of spurious and substandard pharmaceutical products, the Committee affirmed that high priority should be accorded to the development of simple or basic tests for verifying the identity of pharmaceutical substances and dosage forms. Details of many tests have been published (*4*, *5*), and further tests for widely available dosage forms have recently been developed. The Committee noted, in particular, that visual inspection was accorded due importance, and it suggested that complementary tests should be developed to detect or exclude gross degradation.

6.4 National laboratories for drug surveillance and control

Recommendations on the staffing and organization of two types of model drug quality control laboratories designed specifically for developing countries were included in the Committee's twenty-ninth report, published in 1984 (*6*). The Committee noted that the estimated capital cost of the specified equipment had since been regularly updated by the Secretariat, and it recommended that the supplies and materials necessary for the continued operation and maintenance of these laboratories should also be estimated and costed and updated in the same way in order to provide a more comprehensive indication of overall running costs.

6.5 Quality control of products derived from medicinal plants

The Committee underscored the need to develop recommendations on the quality control of plant material, particularly having regard to increasing demand and international trade in traditional medicines and "natural products". Whereas it is usually possible to identify and evaluate individual plants and products derived from them, it is difficult to standardize a formulation containing a number of plants or their components.

The Committee recommended that general recommendations on the quality assurance of medicinal plant products should be issued by WHO and that specialists in the field should be consulted before draft documents are finalized. Attention should first be directed to establishing the availability of selected medicinal plants before determining criteria for their identification and evaluation. Standardization of compound formulations should be deferred to a future phase of the activity.

The intention of UNIDO to collaborate closely with WHO in this field was noted.

7. International Chemical Reference Substances and International Infrared Reference Spectra

7.1 Establishment of reference substances

The Committee revised the procedure for establishing International Chemical Reference Substances, as set out in its thirty-first report (*7*), and additionally recommended the following:

> Newly established International Chemical Reference Substances, proposed by the WHO Collaborating Centre for Chemical Reference Substances on the basis of adequate testing and characterization, are included in the Centre's annual report. The report is circulated, *inter alia,* to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, who are requested to consider the proposals carefully together with the attached analytical documentation, and to notify the Centre of any reservations or adverse comments within three months of the date of mailing. In these cases the Centre will proceed with any consultations or additional analyses necessary for the validation.
>
> If no adverse comments are received within the three-month period, the proposed new International Chemical Reference Substance may be considered *provisionally* adopted. It will be considered for *final* adoption during the subsequent meeting of the Expert Committee.

The Committee expressed its appreciation to the WHO Collaborating Centre for its work and noted with satisfaction that collaboration with other laboratories, and particularly that of the European Pharmacopoeia, had been sustained. Seven new International Chemical Reference Substances were adopted by the Committee,[1] which noted that, since its thirty-first meeting, replacement batches had also been introduced for eight previously established Reference Substances. The total collection now comprises 147 International Chemical Reference Substances and 13 Melting-Point Reference Substances (Annex 6).

In order to promote more efficient use of International Chemical Reference Substances, the Committee recommended that the "General guidelines for the establishment, maintenance, and distribution of chemical reference substances" (*8*), which were first issued in 1982, be revised. It suggested that more information be provided on establishing, calibrating, and using secondary reference materials and that existing advice on their certification be extended. Consideration should also be given to modifying some of the recommended methods for characterizing reference substances.

[1] Chlortetracycline hydrochloride, clomifene citrate, clomifene citrate *Z*-isomer (zuclomifene), emetine hydrochloride, neostigmine metilsulfate, propranolol hydrochloride, and sodium cromoglicate.

7.2 Infrared reference spectra

The Committee noted with satisfaction recent progress made in the provision of International Infrared Reference Spectra, which are intended to be used in connection with monographs of *The international pharmacopoeia* to confirm the identity of specific substances. The first group of 40 spectra were prepared in a pilot phase by the School of Pharmacy, Federal Institute of Technology, Zurich, Switzerland. The spectra were subsequently evaluated by 15 governmental and independent drug quality control laboratories and then reviewed by members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations. The first group of 40 spectra was finally adopted by the Expert Committee at its present meeting, and the Committee recommended that this procedure be established as a basis for the adoption of further spectra. It endorsed plans to issue a short guide on the use of International Infrared Reference Spectra and it undertook to review the project in the light of further experience.

The spectra listed in Annex 7 will shortly be available from the WHO Collaborating Centre for Chemical Reference Substances, Stockholm, Sweden.

8. Stability of dosage forms

The Committee noted that, further to discussions during its thirty-first meeting, some preliminary information on products associated with stability problems had been obtained from national drug regulatory authorities. It endorsed plans for a second, more detailed survey to be undertaken on products of questionable stability included in the Model List of Essential Drugs published by WHO. An attempt will be made to obtain an indication of the frequency with which stocks of specific products are detected as substandard and rejected; to obtain precise information on the causes of defects whenever possible; and to correlate the various types of defect with prevailing climatic conditions. Every effort will be made to distinguish between defects that result from unsatisfactory formulation and those caused by inappropriate storage.

The objectives of the survey are twofold. The results will be used in the first instance to alert manufacturers, distributors, and drug regulatory authorities to the precise nature and magnitude of any problems that become apparent. They will then be used to formulate advice on packaging and storage and, in some cases, to rank products within a particular therapeutic class according to their stability characteristics.

The Committee also strongly endorsed the Secretariat's plans to conduct a study jointly with UNICEF on the wider issue of the quality of selected products at the point of use in developing countries. The detailed protocol is provided in Annex 8. The Committee emphasized the necessity for all

drug manufacturers and everyone holding a responsibility for the subsequent distribution of both starting materials and finished products to take every reasonable precaution to assure the quality of the product up to the time of administration or delivery to the patient or consumer.

9. Extemporaneous preparations

9.1 Topical dosage forms

The Committee accepted that pharmacists are still frequently called upon, particularly in developing countries, to prepare small quantities of specific dosage forms to meet short-term local requirements. While in no circumstance condoning the formulation of drugs – particularly those that need to be sterile – in inadequate facilities, it acknowledged that an authoritative manual on the extemporaneous preparation of non-sterile topical dosage forms should be available to pharmacists or health personnel involved with this work.

The Committee insisted that, in meeting this need, recommendations must be explicitly directed and exclusively channelled to compounding/dispensing pharmacists and not to commercial manufacturers, since effective quality assurance must be depicted as a mandatory component of the manufacturing process. It suggested that the general principles at issue should be subjected to further consultation before work is undertaken on a definitive handbook.

9.2 The local small-scale preparation of ophthalmic (eye) drops

Within the same general context, the Committee reviewed proposals on the local small-scale preparation of eye drops that had been drafted by a WHO working group (*9*). It accepted that, when topical ophthalmic preparations in the Model List of Essential Drugs are not available, the delivery of basic eye care is frustrated. In these circumstances, which are frequently encountered, the only practicable expedient is to arrange for specific preparations to be produced in local hospitals, using simple but adequate methods, under the supervision of an appropriately experienced pharmacist. The Committee considered it important that any guidelines concerned with such practices should be issued exclusively to pharmacists and health care facilities serving the populations in need.

Because of the serious consequences that can arise from microbial contamination, extreme care is needed in the production and subsequent handling of eye drops. Local production should always be undertaken on a scale sufficiently small to assure both initial sterility and rapid turnover of the product. In every instance, careful consideration should be given to the cost-effectiveness of the manufacturing process and the adequacy of the arrangements for quality control.

10. Training of regulators

The Committee expressed its conviction that the first need in developing national competence in drug control is the training of key staff in every aspect of regulation and enforcement. It recognized that international coordination of training programmes and of the production of educational materials is essential to success. Priority, it suggested, should be accorded to the following elements:

- *Budgeting for and management of small quality control laboratories.* The twenty-ninth report of the Committee (*4*) provides specifications for two types of small national laboratories for drug quality control. The arguments for establishing such laboratories in countries that do not yet possess them remain persuasive. Equally important is the need to develop the management capability of the laboratory directors since it is imperative that all capital expenditure and running costs should be efficiently rationalized and securely budgeted.
- *Training of laboratory technicians.* Locally trained technicians are of critical importance in routine analytical work. However, since they need specific training in pharmacopoeial methods, it is vital that the larger laboratories already established in developing countries should serve as regional or subregional centres able to offer suitable group training.
- *Maintenance of equipment.* The maintenance of complex equipment creates major difficulties if the manufacturer has no servicing facility within the country. Where this problem exists, arrangements must be made to train local technicians to undertake essential routine servicing.
- *Promotion of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.* Now that guidelines for use of the proposed extended Scheme are ready for adoption, it is vital that training seminars and workshops be organized to promote the use of the Scheme.

The Committee underscored the importance of the support that various nongovernmental organizations, including the German Foundation for International Development, the International Federation of Pharmaceutical Manufacturers Associations and the WHO Collaborating Centre for Chemical Reference Substances, continue to give to vital training programmes for drug regulators.

11. Arrangements for independent analysis of drug samples

In the case of a dispute arising from an unanticipated adverse reaction to a drug or from physical signs of deterioration in the product, a country may need to turn to a foreign laboratory for analytical confirmation of a presumed defect. The Committee endorsed the efforts of the Secretariat to create a network of collaborating national laboratories ready, under

specified conditions, to undertake confirmatory analyses. It is hoped that these arrangements can be extended to all products covered by the WHO Certification Scheme and that, when such analyses have undisputed implications for public health, directors of laboratories within the network will have discretionary authority to undertake them at cost or even free of charge.

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[1] The fifth report of the WHO Expert Committee on the Use of Essential Drugs, which met in November 1991, will be published as WHO Technical Report Series, No. 825.

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9. *The local small-scale preparation of eye drops.* Geneva, World Health Organization, 1990 (unpublished document WHO/PBL/90.20; available on request from Programme for the Prevention of Blindness, World Health Organization, 1211 Geneva 27, Switzerland).

Annex 1

Good manufacturing practices for pharmaceutical products

Introductory note

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

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

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

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

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

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

- *Guide to good pharmaceutical manufacturing practice 1983.* London, Her Majesty's Stationery Office, 1983 ("Orange Guide"). [Superseded by the 1992 EEC guide.]
- *Bonnes pratiques de fabrication et de production pharmaceutiques.* Paris, Ministère des Affaires Sociales et de la Solidarité Nationale, Secrétariat d'Etat chargé de la Santé, Direction de la Pharmacie et du Médicament, 1985. [Superseded by the 1992 EEC guide.]
- *ASEAN good manufacturing practices guidelines,* 2nd ed. Association of South East Asian Nations, 1988.

- *Good manufacturing practice for medicinal products in the European Community.* Commission of the European Communities, 1992.
- *Guide to good manufacturing practice for pharmaceutical products.* Convention for the Mutual Recognition of Inspection in Respect of the Manufacture of Pharmaceutical Products (PIC), 1992.

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

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

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

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

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

General considerations

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

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

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

Glossary

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

packaging material
Any material, including printed material, employed in the packaging of a

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

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

processing instructions
See master formula.

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

quality assurance
See Part One.

quality control
See Part One.

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

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

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

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

returned product
Finished product sent back to the manufacturer.

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

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

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

system
A regulated pattern of interacting activities and techniques that are united to form an organized whole.

validation
The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Part One. Quality management in the drug industry: philosophy and essential elements

In the drug industry at large, quality management is defined[1] as the aspect of management function that determines and implements the "quality policy", i.e., the overall intentions 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; and
- 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".

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

[1] This definition conforms with that contained in International Standard ISO 9000.

In drug manufacture and supply the terminology may differ. In particular, the term "quality system" is rarely used, and it is "quality assurance" that usually embraces such elements as organizational structure, procedures, and processes.

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)[1] 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 section 10.6) have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products;

[1] 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).

(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.

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 rules are directed primarily to diminishing the risks, inherent in any pharmaceutical production, that cannot be prevented completely through the testing of final products. Such risks are essentially of two types: cross-contamination (in particular by unexpected contaminants) and mix-ups (confusion) caused by 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) critical steps of manufacturing processes and any significant changes made to the processes are validated;
(c) all necessary facilities are provided, including:
    (i) appropriately qualified and trained personnel;
    (ii) adequate premises and space;
    (iii) suitable equipment and services;
    (iv) correct materials, containers, and labels;
    (v) approved procedures and instructions;
    (vi) suitable storage and transport; and

(vii) adequate personnel, laboratories, and equipment for in-process controls under the responsibility of the production management;

(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 and to prevent recurrence.

3. Quality control

3.1 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.

3.2 Each holder of a manufacturing authorization should have a quality control department.[1] The independence of quality control from production is considered fundamental. The quality control department should be independent 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.

[1] Except for a holder performing only a fraction of the manufacturing process under a contract (see section 8).

(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) Test methods must be validated.
(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 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 the production department together with the authorized person from the quality control department.
(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.

3.3 The quality control department 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.

3.4 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.

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

4. Sanitation and hygiene

4.1 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 *hygiene* please refer to section 10, "Personnel", and for *sanitation* to section 11, "Premises".)

5. Validation

5.1 Validation studies are an essential part of GMP and should be conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions should be prepared and stored. Processes and procedures should be established on the basis of a validation study and undergo periodic revalidation to ensure that they remain capable of achieving the intended results. Particular attention should be accorded to the validation of processing, testing, and cleaning procedures.

Process validation

5.2 Critical processes should be validated, prospectively or retrospectively.

5.3 When any new master formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.4 Significant amendments to the manufacturing process, including any change in equipment or materials that may affect product quality and/or the reproducibility of the process, should be validated.

6. Complaints

6.1 *Principle.* All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures.

6.2 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.

6.3 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.

6.4 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 study of such problems.

6.5 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.

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

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

6.8 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.

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

7. Product recalls

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

7.2 A person responsible for the execution and coordination of recalls should be designated, as well as sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency. This person should normally be independent of the sales and marketing organization. If this person is different from the authorized person, the latter should be made aware of any recall operation.

7.3 There should be established written procedures, regularly checked and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly at least down to the level of the hospital or pharmacy.

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

7.5 The distribution records should be readily available to the person(s) responsible for recalls, 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.

7.6 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.

7.7 The effectiveness of the arrangements for recalls should be evaluated from time to time.

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

8. Contract production and analysis

8.1 *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. There must be a written contract between the contract giver and the contract accepter which clearly establishes the duties of each party. 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.

General

8.2 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.

8.3 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

8.4 The contract should permit the contract giver to audit the facilities of the contract accepter.

8.5 In the case of contract analysis, the final approval for release must be given by the authorized person(s).

The contract giver

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

8.7 The contract giver should provide the contract accepter with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract accepter 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.

8.8 The contract giver should ensure that all processed products and materials delivered by the contract accepter comply with their specifications or that the product has been released by the authorized person(s).

The contract accepter

8.9 The contract accepter 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.

8.10 The contract accepter 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 accepter 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 accepter.

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

The contract

8.12 A contract should be drawn up between the contract giver and the contract accepter that specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis, and GMP. All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

8.13 The contract should specify the way in which the authorized person releasing the batch for sale ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

8.14 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 accepter should take samples at the premises of the manufacturer.

8.15 Manufacturing, analytical, and 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.

8.16 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 processing of information if the contract analysis shows that the tested product must be rejected.

9. Self-inspection and quality audits

9.1 *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

9.2 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
(l) recall procedures
(m) complaints management
(n) labels control
(o) results of previous self-inspections and any corrective steps taken.

Self-inspection team

9.3 Management should appoint a self-inspection team from local staff who are expert in their own fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

9.4 The frequency at which self-inspections are conducted may depend on company requirements.

Self-inspection report

9.5 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

9.6 The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

9.7 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 8, "Contract production and analysis").

Suppliers' audits

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

9.9 Before suppliers are approved and included in the 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 for active pharmaceutical ingredients (see section 18).

10. Personnel

10.1 *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 understood by the individuals concerned and recorded

as written descriptions. All personnel should be aware of the principles of GMP that affect them.

General

10.2 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 as to present any risk to quality.

10.3 The manufacturer should have an organization chart. 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.

10.4 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.

10.5 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.

Key personnel

10.6 Key personnel include the head of production, the head of quality control, the head of sales/distribution, and the authorized person(s). 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.

10.7 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, or (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.

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

(a) the authorization of written procedures and other documents, including amendments;
(b) the 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) the approval and monitoring of suppliers of materials;
(g) the approval and monitoring of contract manufacturers;
(h) the designation and monitoring of storage conditions for materials and products;
(i) the retention of records;
(j) the monitoring of compliance with GMP requirements;
(k) the inspection, investigation, and taking of samples, in order to monitor factors that may affect product quality.

10.9 The head of the production department 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 before they are made available to the quality control department;
(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.

10.10 The head of the quality control department generally has the following responsibilities:

(a) to approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products;
(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 done;
(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 department are summarized in section 3.2.

Training

10.11 The manufacturer should provide training in accordance with a written programme for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance, and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

10.12 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 should be periodically assessed. Training programmes should be available, approved by the head of either production or quality control, as appropriate. Training records should be kept.

10.13 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.

10.14 The concept of quality assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

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

Personal hygiene

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

10.17 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.

10.18 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.

10.19 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.

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

10.21 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.

10.22 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.

10.23 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.

11. Premises

11.1 *Principle.* Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. Their layout and design 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.

General

11.2 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.

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

11.4 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. Premises should be cleaned and, where applicable, disinfected according to detailed written procedures.

11.5 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.

11.6 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

Ancillary areas

11.7 Rest and refreshment rooms should be separate from other areas.

11.8 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.

11.9 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.

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

Storage areas

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

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

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

11.14 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.

11.15 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.

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

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

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

***Weighing areas** (may belong to either storage or production areas)*

11.19 The weighing of starting materials and the estimation of yield by weighing should usually be carried out in separate weighing areas designed for that use, for example with provisions for dust control.

Production area

11.20 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 products, such as some antibiotics, hormones, cytotoxic substances, highly active pharmaceutical products, and non-pharmaceutical products, should not be conducted in the same facilities. The manufacture of technical poisons, such as pesticides and herbicides, should not normally be allowed in premises used for the manufacture of pharmaceutical products. 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 are made.

11.21 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.

11.22 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.

11.23 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.

11.24 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.

11.25 Drains should be of adequate size 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.

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

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

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

Quality control area

11.29 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.

11.30 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), and records.

11.31 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes, and ventilation. Separate air-handling units and other provisions are needed for biological, microbiological, and radioisotope laboratories.

11.32 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.

12. Equipment

12.1 *Principle.* 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.

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

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

12.4 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.

12.5 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.

12.6 Production equipment should be designed, located, and maintained to serve its intended purpose.

12.7 Production equipment should be designed so that it can be easily and thoroughly cleaned on a scheduled basis.

12.8 Control-laboratory equipment and instruments should be suited to the testing procedures undertaken.

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

12.10 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.

12.11 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

13. Materials

13.1 *Principle.* The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (active, auxiliary, packaging). Special attention should be given to the materials as such.

General

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

13.3 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-in, first-out rule.

Starting materials[1]

13.4 The purchase of starting materials is an important operation that

[1] Please refer also to Part Three, section 18.

should involve staff who have a particular and thorough knowledge of the products and suppliers.

13.5 Starting materials should be purchased only from suppliers named in the relevant specification 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 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 discussed between the manufacturer and the supplier.

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

13.7 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed data.

13.8 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.

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

13.10 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(s) given by the supplier and on receipt by the manufacturer, if any;
(c) where appropriate, 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 computerized storage systems are used, not all of the above information need be in a legible form on the label.

13.11 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.

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

13.13 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.

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

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

Packaging materials

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

13.17 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. 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.

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

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

13.20 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

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

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

Finished products

13.23 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

13.24 The evaluation of finished products and the documentation necessary for release of a product for sale are described in section 16, "Good practices in quality control".

Rejected and recovered materials

13.25 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. Whatever action is taken should be approved by authorized personnel and recorded.

13.26 The reprocessing 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 of the reprocessing. A reprocessed batch should be given a new batch number.

13.27 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.

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

Recalled products

13.29 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

13.30 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; they may be considered for resale, relabelling, or bulking with a subsequent batch only after they have been critically assessed by the quality control department 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, although basic chemical reprocessing to recover the active ingredient may be possible. Any action taken should be appropriately recorded.

Reagents and culture media

13.31 All reagents and culture media should be recorded upon receipt or preparation.

13.32 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.

13.33 Both positive and negative controls should be applied to verify the suitability of culture media. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference standards

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

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

13.36 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization. All in-house reference standards should be based on official reference standards, when available.

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

Waste materials

13.38 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.

13.39 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

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

14. Documentation

14.1 *Principle.* Good documentation is an essential part of the quality assurance system and, as such, should be related to all aspects of GMP. Its aims are to define the specifications 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, and to provide an audit trail that will permit investigation of the history of any suspected defective batch. 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

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

14.3 Documents should be approved, signed, and dated by appropriate authorized persons. No document should be changed without authorization.

14.4 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.

14.5 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.

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

14.7 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.

14.8 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 and associated standard operating procedures should be retained for at least one year after the expiry date of the finished product.

14.9 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.

Documents required

Labels

14.10 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 (for example: quarantined, accepted, rejected, or clean).

14.11 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 International Nonproprietary Names), showing the amount of each present, and a statement of the net contents, e.g., number of dosage units, weight, or 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; and
(g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

14.12 For reference standards, the label or accompanying document should indicate concentration, date of manufacture, expiry date, date the closure is first opened, and storage conditions, where appropriate.

Specifications and testing procedures

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

14.14 There should be appropriately authorized and dated specifications, including tests on identity, content, purity, and quality, for starting and packaging materials and 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.

14.15 Each specification should be approved and maintained by the quality control unit. Specifications for starting materials, intermediates, and bulk and finished products are referred to in sections 14.18-14.21.

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

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

Specifications for starting and packaging materials

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

(a) the designated name (if applicable, the International Nonproprietary Name) and internal code reference;
(b) the reference, if any, to a pharmacopoeial monograph; and
(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, with emphasis placed on the compatibility of the material with the drug product it contains. The material should be examined for critical and major physical defects as well as for the correctness of identity markings.

14.19 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

14.20 Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used in the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

14.21 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, the International Nonproprietary Name(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; and
(h) the shelf-life.

Master formulae

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

14.23 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 International Nonproprietary Names), 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 the critical equipment, e.g., cleaning (especially after a change in product), assembling, calibrating, sterilizing;
(g) detailed stepwise processing instructions (e.g., checks on materials, pretreatments, 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

14.25 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 method of application where applicable;
(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 operations begin;
(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

14.26 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved master formula. The method of preparation of such records should be designed to avoid transcription errors.

14.27 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.

14.28 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;
(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

14.29 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the packaging instructions, and the method of preparing such records should be designed to avoid transcription errors.

14.30 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.

14.31 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;
(g) whenever possible, samples of the printed packaging materials used, including specimens bearing 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

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

14.33 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).

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

14.35 Standard operating procedures should be available for each instrument and piece of equipment and placed in close proximity to the equipment.

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

14.37 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;
(g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

14.38 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.

14.39 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.

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

14.41 Batch-number allocation should be immediately recorded, e.g., in a logbook. The record should include date of allocation, product identity, and size of batch.

14.42 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.

14.43 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) dates of testing;
(f) the initials of the persons who performed the testing;
(g) the initials of the persons who verified the testing and the calculations, where appropriate;
(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

14.44 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.

14.45 Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

14.46 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.

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

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

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

Part Two. Good practices in production and quality control

15. Good practices in production[1]

15.1 *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

15.2 All handling of materials and products, such as receipt and quar-

[1] For the manufacture of sterile products please refer to Part Three, section 17. For the manufacture of active pharmaceutical ingredients (bulk drug substances) please refer to Part Three, section 18.

antine, sampling, storage, labelling, dispensing, processing, packaging, and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

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

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

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

15.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate the rooms 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.

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

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

15.9 In-process controls are mostly performed within the production area. They should not carry any risk for the quality of the product.

Prevention of cross-contamination and bacterial contamination in production

15.10 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust.

15.11 Contamination of a starting material or of a product by another material or product has to be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, 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.

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

(a) production in segregated areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
(b) providing appropriate airlocks, pressure differentials, and air extraction;
(c) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
(d) wearing protective clothing in areas where products with special risk of cross-contamination are processed;
(e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
(f) using a "closed system" of production;
(g) testing for residues;
(h) using cleanliness status labels on equipment.

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

15.14 Production areas where susceptible products are processed should undergo periodic microbiological monitoring.

Processing operations: intermediate and bulk products

15.15 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.

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

15.17 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. Production equipment should be cleaned according to detailed written procedures and stored only under clean and dry conditions.

15.18 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.

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

15.20 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.

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

15.22 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.

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

Packaging operations

15.24 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.

15.25 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 previously used and not required for the current operation. The line clearance should be performed according to an appropriate checklist and recorded.

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

15.27 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.

15.28 The correct performance of any printing (for example 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.

15.29 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 readers, label counters, or similar devices are operating correctly.

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

15.31 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.

15.32 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.

15.33 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 and satisfactorily accounted for before release.

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

16. Good practices in quality control

16.1 *Principle.* Quality control is concerned with sampling, specifications, and testing as well as with the organization, documentation, and release procedures that ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality control is not confined to laboratory operations, but must be involved in all decisions that may concern the quality of the product. The independence of quality control from production is considered fundamental.[1]

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

16.2 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.

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

16.4 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.

[1] Please refer also to Part One, section 3.

16.5 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.

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

16.7 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 signature of the person who has taken the sample; and
(e) the date of sampling.

Test requirements

Starting and packaging materials

16.8 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.

16.9 An identity test should be conducted on a sample from each container of starting material (see also section 13.11).

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

16.11 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 9.8 and 9.9) and through on-site audits of the supplier's capabilities. (This does not affect section 16.9). Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain the following information:

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

In-process control

16.12 In-process control records should be maintained and form a part of the batch records (see section 15.2).

Finished products

16.13 For each batch of drug product, there should be an appropriate

laboratory determination of satisfactory conformity to its finished product specification prior to release.

16.14 Products failing to meet the established specifications or any other relevant quality criteria should be rejected. Reprocessing may be performed, if feasible, but the reprocessed product should meet all specifications and other quality criteria prior to its acceptance and release.

Production record review[1]

16.15 Production and control records should be reviewed and 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.

16.16 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

16.17 The quality control department should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

16.18 The quality control department should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

16.19 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 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;

[1] Also known as batch review.

(f) provision for adequate sample retention; and
(g) a summary of all the data generated, including the evaluation and the conclusions of the study.

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

Part Three. Supporting and supplementary guidelines

17. Sterile pharmaceutical products

Explanation

These guidelines do not replace any of the sections in Parts One and Two but stress specific points for the manufacture of sterile preparations to minimize the risks of microbiological, particulate, and pyrogen contamination.

General

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

17.2 The various operations of component preparation (such as containers and closures), product preparation, filling, and sterilization should be carried out in separate areas within the clean area.

17.3 Clean areas for the production of sterile products are classified according to the required characteristics of the air, in grades A, B, C, and D (see Table 1).

Table 1
Air classification system for manufacture of sterile products

Grade	Maximum number of particles permitted per m^3		Maximum number of viable microorganisms permitted per m^3
	0.5–5 μm	>5 μm	
A (Laminar-airflow workstation)	3 500	none	less than 1
B	3 500	none	5
C	350 000	2 000	100
D	3 500 000	20 000	500

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

- Laminar-airflow systems should provide a homogeneous air speed of about 0.30 m/s for vertical flow and about 0.45 m/s for horizontal flow but precise air speeds will depend on the type of equipment.
- In order to reach the B, C, and D air grades, the number of air changes should generally be higher than 20 per hour in a room with a good airflow pattern and appropriate HEPA (high-efficiency particulate air) filters.
- Low values for contaminants are reliable only when a large number of air samples are taken.
- The guidance given for the maximum permitted number of particles corresponds approximately to the United States Federal Standard 209E (1992) as follows: Class 100 (grades A and B), Class 10 000 (grade C), and Class 100 000 (grade D).

It may not always be possible to demonstrate conformity with particular air standards at the point of fill when filling is in progress, owing to the generation of particles or droplets from the product itself.

17.4 Each manufacturing operation requires an appropriate air cleanliness level in order to minimize the risks of particulate or microbial contamination of the product or materials being handled. Section 17.5 gives the minimum air grades required for different manufacturing operations. The particulate and microbiological conditions given in Table 1 should be maintained in the zone immediately surrounding the product whenever the product is exposed to the environment. These conditions should also be achieved throughout the background environment if no personnel are present in the processing area, and if the standards fall for any reason it should be possible to recover the conditions after a short "clean-up" period. The utilization of absolute-barrier technology and automated systems to minimize human interventions in processing areas can produce significant advantages in ensuring the sterility of manufactured products. When such techniques are used, the recommendations in these supplementary guidelines, particularly those relating to air quality and monitoring, still apply, with appropriate interpretations of the terms "workstation" and "environment".

Manufacture of sterile preparations

17.5 Manufacturing operations are here divided into three categories: first, those in which the preparation is sealed in its final container and terminally sterilized; second, those in which the preparation is sterilized by filtration; and third, those in which the preparation can be sterilized neither by filtration nor terminally and consequently must be produced from sterile starting materials in an aseptic way. Area grades as specified in

sections 17.5.1-17.5.3, must be selected by the manufacturer on the basis of validation runs (e.g., sterile media fills).

Terminally sterilized products

17.5.1 Solutions should generally be prepared in a grade C environment in order to give low microbial and particulate counts, suitable for immediate filtration and sterilization. Solution preparation could be allowed in a grade D environment if additional measures were taken to minimize contamination, such as the use of closed vessels. For parenterals, filling should be done in a laminar-airflow workstation (grade A) in a grade C environment. The preparation of other sterile products, e.g., ointments, creams, suspensions, and emulsions, and filling of containers should generally be done in a grade C environment before terminal sterilization.

Sterile filtered products

17.5.2 The handling of starting materials and the preparation of solutions should be done in a grade C environment. These activities could be allowed in a grade D environment if additional measures were taken to minimize contamination, such as the use of closed vessels prior to filtration. After sterile filtration, the product must be handled and dispensed into containers under aseptic conditions in a grade A or B area with a grade B or C background respectively.

Other sterile products prepared from sterile starting materials in an aseptic way

17.5.3 The handling of starting materials and all further processing should be done in a grade A or B area with a grade B or C background respectively.

Personnel

17.6 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 the areas as far as possible.

17.7 All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products, including reference to hygiene and to 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 supervision.

17.8 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.

17.9 High standards of personal hygiene and cleanliness are essential, and personnel involved in the manufacture of sterile preparations should be instructed to report any condition that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person.

17.10 Outdoor clothing should not be brought into the clean areas, and personnel entering the changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a written procedure.

17.11 The clothing and its quality has to be adapted to the process and the workplace, and worn in such a way as to protect the product from contamination.

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

17.13 Clothing should be appropriate to the air grade of the area where the personnel will be working. The description of clothing required for each grade is given below.

Grade D: The hair and, where appropriate, beard should be covered. Protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

Grade C: The hair and, where appropriate, beard 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.

Grade B: Headgear should totally enclose the hair and, where appropriate, beard; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets; 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.

17.14 For every worker in a grade B room, clean sterilized protective garments should be provided at each work session, or at least once a day if monitoring results justify it. Gloves should be regularly disinfected during operations, and masks and gloves should be changed at least at every working session. The use of disposable clothing may be necessary.

17.15 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.

Premises

17.16 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.

17.17 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.

17.18 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.

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

17.20 Pipes and ducts should be installed so that they do not create recesses that are difficult to clean.

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

17.22 Changing rooms should be designed as airlocks and used to provide separation of the different stages of changing, so minimizing microbial and particulate 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 desirable. Hand-washing facilities should be provided only in the changing rooms, not in areas where aseptic work is done.

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

Equipment

17.24 A filtered air supply should maintain a positive pressure relative to

surrounding areas under all operational conditions and flush the area effectively. Moreover, particular attention should be paid to the protection of the zone of greatest risk, that is, 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 if it becomes necessary to contain materials such as pathogenic, highly toxic, radioactive, or live viral or bacterial materials. Decontamination facilities and the treatment of air leaving a clean area may be necessary for some operations.

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

17.26 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.

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

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

17.29 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.

17.30 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.

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

17.32 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.

17.33 Water-treatment plants should be designed, constructed, and maintained so as to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water should be produced, stored, and distributed in a manner

that prevents microbial growth – for example, by constant circulation at 80 °C or not more than 4 °C.

Sanitation

17.34 The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with a written programme approved by the quality control department. Where disinfectants are used, more than one type should be employed, with periodic alterations. 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.

17.35 Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should not be stored for long periods unless sterilized. Partly emptied containers should not be topped up.

17.36 Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

17.37 Clean areas should be monitored at planned intervals during operations by means of microbial counts of air and surfaces; where aseptic operations are performed, monitoring should be frequent to ensure that the environment is within specifications. The results of monitoring should be considered when batches are assessed for approval. Air particulate quality should also be evaluated on a regular basis. Additional monitoring is sometimes desirable even when there are no production operations, e.g., after validation of systems, cleaning, and fumigation.

Processing

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

17.39 Preparations containing live microbiological organisms should not be made or containers filled in areas used for the processing of other pharmaceutical products; however, vaccines 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.

17.40 The use of nutrient media that support microbial growth in trials to simulate aseptic operations (sterile media fills, "broth fills") is a valuable part of overall validation of an aseptic process. Such trials should have the following characteristics:

(a) They should simulate as closely as possible actual operations, taking into account such factors as complexity of operations, number of personnel working, and length of time.

(b) The medium or media selected should be capable of growing a wide spectrum of microorganisms, including those that would be expected to be found in the filling environment.
(c) They should include a sufficient number of units of production to give a high degree of assurance that low levels of contamination, if present, would be detected.

It is recommended that at least 3000 units of production be included in each broth-fill trial. The target should be zero growth and anything above 0.1% of units contaminated should be considered unacceptable. Any contamination should be investigated. Broth fills should be repeated at regular intervals, and whenever a significant alteration in the product, premises, equipment, or process warrants revalidation.

17.41 Care should be taken that validations do not harm the processes.

17.42 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.

17.43 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, 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.

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

17.45 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.

17.46 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.

17.47 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.

17.48 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.

17.49 Any gas that is used to purge a solution or blanket a product should pass through a sterilizing filter.

17.50 The microbiological contamination of products ("bioburden") should be minimal prior to sterilization. There should be a working limit on contamination 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 microbial air filters.

17.51 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 achieve the same end of not introducing contamination (e.g., triple wrapping) may be acceptable in some circumstances.

17.52 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.

Sterilization

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

17.54 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. In any case, the sterilization process must be in accordance with the marketing and manufacturing authorizations.

17.55 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. This work should be repeated at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

17.56 Biological indicators should be considered only as an additional method for monitoring the sterilization. If they are used, strict precautions should be taken to avoid transferring microbial contamination from them.

17.57 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 lot is, in fact, sterile.

Sterilization by heat

17.58 Each heat sterilization cycle should be recorded by appropriate equipment with suitable accuracy and precision, e.g., on a time/temperature chart with a suitably large scale. The temperature should be recorded from 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.

17.59 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.

17.60 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, unless it can be shown that any leaking container would not be approved for use.

Sterilization by moist heat

17.61 Sterilization by moist heat is suitable only for water-wettable materials and aqueous solutions. 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 is 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.

17.62 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows removal of air and 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.

17.63 Care should be taken to ensure that 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

17.64 The process used for sterilization by dry heat 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. Where this process of sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins would be required as part of the validation.

Sterilization by radiation

17.65 Radiation sterilization 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.

17.66 If radiation sterilization is carried out by an outside contractor, the manufacturer has the responsibility of ensuring that the requirements of section 17.65 are met, and that the sterilization process is validated. The responsibilities of the radiation plant operator (e.g., for the right dose) should also be specified.

17.67 During the sterilization procedure the radiation dose should be measured. For this purpose, dosimeters that are independent of dose rate should be used, giving 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 used, they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period 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.

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

17.69 Handling procedures should prevent any mix-up between 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.

17.70 The total radiation dose should be administered within a predetermined time span.

Sterilization by ethylene oxide

17.71 Various gases and fumigants may be used for sterilization. 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. These limits should be incorporated into the specifications.

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

17.73 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilization.

17.74 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.

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

17.76 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 throughout the cycle on a chart. The records should form part of the batch record.

17.77 After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to fall to the defined level. This process should be validated.

Filtration of pharmaceutical products that cannot be sterilized in their final container

17.78 Whenever possible, products should be sterilized in the final container, preferably by heat sterilization. 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 μm (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.

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

17.80 Filters that shed fibres should not be used. The use of asbestos-containing filters should be absolutely excluded.

17.81 The integrity of the filter should be checked by an appropriate method such as a bubble point test immediately after each 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 this should be noted and investigated. Results of these checks should be recorded in the batch record.

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

17.83 The filter should not affect the product by removal of ingredients from it or by release of substances into it.

Finishing of sterile products

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

17.85 Containers sealed under vacuum should be sampled and the samples tested for maintenance of that vacuum after an appropriate predetermined period.

17.86 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.

Quality control

17.87 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 the potentially coolest part of the load.

17.88 The sterility test applied to the finished product should be regarded only as the last in a series of control measures by which sterility is assured and can be interpreted only in conjunction with the environmental and batch processing records.

17.89 Batches failing an initial sterility test should not be released on the basis of a second test unless an investigation into the type of organism found, and into the environmental and batch processing records involved, show that the original test was invalid.

17.90 For injectable products, consideration should be given to monitoring the water and the intermediate and finished product 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 the marketing authorization on the finished product. When a sample fails a test, the cause of failure should be investigated and remedial action taken where necessary.

18. Good manufacturing practices for active pharmaceutical ingredients (bulk drug substances)

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 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.

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, multi-purpose 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.

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 differents 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.

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;
    (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.

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.

Annex 2

Provisional guidelines on the inspection of pharmaceutical manufacturers

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 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.

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[1]

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.

[1] 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.
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 accepter 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-inspection

9.1 Short description of the self-inspection system.

Annex 3

Proposed guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce[1]

1. Provisions and objectives

1.1 A comprehensive system of quality assurance must be founded on a reliable system of licensing[2] and independent analysis of the finished product, as well as on an assurance obtained through independent inspection that all manufacturing operations are carried out in conformity with accepted norms, referred to as "good manufacturing practices" (GMP).

1.2 In 1969, the Twenty-second World Health Assembly, by resolution WHA22.50, endorsed requirements for "Good practices in the manufacture and quality control of drugs" (*1*) (referred to henceforth as "GMP as recommended by WHO"). These comprise internationally recognized and respected standards that all Member States are urged to adopt and to apply. They have since been revised twice. The first revision was adopted by the Health Assembly in 1975 in resolution WHA28.65, and a second revision of the requirements was discussed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its meeting in December 1990 (*2*).

1.3 These standards are fully consonant with those operative within the countries participating in the Convention for the Mutual Recognition of Inspection in Respect of the Manufacture of Pharmaceutical Products, and other major industrialized countries. They also provide the basis for the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (*1*) (referred to henceforth as "the Scheme"), recommended initially in resolution WHA22.50. The Scheme is an administrative instrument that requires each participating Member State, upon application by a commercially interested party, to attest to the competent authority of another participating Member State that:

- a specific product is authorized to be placed on the market within its jurisdiction or, if it is not thus authorized, the reason why that authorization has not been accorded;
- the plant in which it is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by WHO; and
- all submitted product information, including labelling, is currently authorized in the certifying country.

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[1] Endorsed by the World Health Assembly in May 1992 in resolution WHA45.29.

[2] Throughout this document "licensing" refers to any statutory system of approval required at national level as a precondition for placing a pharmaceutical product on the market.

1.4 The Scheme, as subsequently amended in 1975 (*3*) and 1988 (*4*) by resolutions WHA28.65 and WHA41.18, is applicable to finished dosage forms of pharmaceutical products intended for administration to human beings or to food-producing animals.

1.5 Provision for certification of active ingredients is also included within the scope of the Scheme. This will be the subject of separate guidelines and certificates.

2. Eligibility for participation

2.1 Any Member State intending to participate in the Scheme may do so by notifying the Director-General of WHO, in writing, of:

- its willingness to participate in the Scheme;
- any significant reservations it intends to observe relating to this participation; and
- the name and address of its national drug regulatory authority or other competent authority.

2.2 These notifications are subsequently announced in the monthly *WHO pharmaceuticals newsletter.* An updated consolidated list will be published annually in the newsletter and will be available to governments at other times from: the Division of Drug Management and Policies, WHO, 1211 Geneva 27, Switzerland.

2.3 A Member State may opt to participate solely to control the *import* of pharmaceutical products and substances. This intention should be stated explicitly in its notification to WHO.

2.4 A Member State intending to use the Scheme to support the *export* of pharmaceutical products should first satisfy itself that it possesses:

- an effective national licensing system, not only for pharmaceutical products, but also for the responsible manufacturers and distributors;
- GMP requirements, consonant with those recommended by WHO, to which all manufacturers of finished pharmaceutical products are required to conform;
- effective controls to monitor the quality of pharmaceutical products registered or manufactured within the country, including access to an independent quality control laboratory;
- a national pharmaceuticals inspectorate, operating as an arm of the national drug regulatory authority, and having the technical competence, experience, and resources to assess whether GMP and other controls are being effectively implemented, and the legal power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;
- the administrative capacity to issue the required certificates, to institute inquiries in the case of complaint, and to notify expeditiously both WHO and the competent authority in any Member State known to have

imported a specific product that is subsequently associated with a potentially serious quality defect or other hazard.

2.5 Each Member State assumes the responsibility to determine, by self-evaluation, whether it satisfies these prerequisites. The Scheme contains no provision, under any circumstance, for external inspection or assessment, either of a competent national authority or of a manufacturing facility.

3. Requesting a certificate

3.1 Three documents can be requested within the scope of the Scheme:

- a Certificate of a Pharmaceutical Product,
- a Statement of Licensing Status of Pharmaceutical Product(s), and
- a Batch Certificate of a Pharmaceutical Product.

3.2 Proposed formats for these documents are provided in Appendices 1, 2, and 3 of these guidelines. All participating countries are urged to adopt these formats to facilitate interpretation of certified information. Requests for the provision of certificates offering more limited attestations – for instance, that the manufacturer complies with GMP or that the product is authorized for "free sale" within the country of export – are discouraged.

3.3 A list of addresses of competent national regulatory authorities participating in the Scheme that are responsible for the registration of pharmaceutical and/or veterinary products, together with details of any reservations they have declared regarding their participation in the Scheme, may be obtained from WHO as indicated in section 2.2.

3.4 The competent authority in each country participating in the Scheme should issue guidelines to all agents responsible for importing pharmaceutical products for human and/or veterinary use that operate under its jurisdiction, including those responsible for public sector purchases, to explain the contribution of certification to the drug regulatory process and the circumstances in which each of the three types of documents will be required.

Certificate of a Pharmaceutical Product

3.5 The Certificate of a Pharmaceutical Product (Appendix 1), issued by the exporting country, is intended for use by the competent authority within an importing country in two situations:

- when the product in question is under consideration for a product licence that will authorize its importation and sale;
- when administrative action is required to renew, extend, vary, or review such a licence.

3.6 All requests for certificates should be channelled through the agent in the importing country and the product-licence holder or other commercially interested party in the exporting country ("the applicant").

The applicant should submit the following information for each product:

- brand name,
- generic name (International Nonproprietary Name where such exists),
- name and address of manufacturing facility,
- formulation (when no product licence exists or when the formulation differs from that of the licensed product),
- product information for medical professionals and for patients as approved in the exporting country,
- labelling on retail and wholesale containers, and
- retail packaging.

3.7 The certificate is a confidential document. As such, it can be issued by the competent authority in the exporting country ("the certifying authority") only with the permission of the applicant and, if different, of the product-licence holder.

3.8 The certificate is intended to be incorporated into a product-licence application in the importing country. Once prepared, it is transmitted to the requesting authority through the applicant and, when applicable, the agent in the importing country.

3.9 When any doubt arises about the status or validity of a certificate, the competent authority in the importing country should request a copy direct from the certifying authority, as provided for in section 4.9 of these guidelines.

3.10 In the absence of any specific agreement, each certificate will be prepared exclusively in the working language(s) of the certifying authority. The applicant will be responsible for providing any notarized translation that may be required by the requesting authority.

3.11 Since the preparation of certificates imposes a significant administrative load on certifying authorities, the service may need to be financed by charges levied upon applicants.

3.12 Supplementary attestations are obtainable only at the discretion of the certifying authority and with the permission of the applicant. The certifying authority is under no obligation to supply additional information. Requests for supplementary information should consequently be referred to the applicant, and only in exceptional circumstances to the certifying authority.

Statement of Licensing Status

3.13 The Statement of Licensing Status of Pharmaceutical Product(s) (Appendix 2) attests only that a licence has been issued for a specified product, or products, for use in the exporting country. It is intended for use by importing agents when considering bids made in response to an international tender, in which case it should be requested by the agent as a condition of bidding. It is intended only to facilitate the screening and

preparation of information. The importation of any product that is provisionally selected through this procedure should be determined on the basis of a Certificate of a Pharmaceutical Product.

Batch Certificate

3.14 The Batch Certificate of a Pharmaceutical Product (Appendix 3) for an individual batch of a pharmaceutical product is normally issued by the manufacturer and only *exceptionally*, as in the case of vaccines, sera and certain other biological products, by the competent authority of the exporting country. The Batch Certificate is intended to accompany and provide an attestation concerning the quality and expiry date of a specific batch or consignment of a product that has already been licensed in the importing country. The Batch Certificate should include the specifications of the final product at the time of batch release and the results of a full analysis undertaken on the batch in question. In most circumstances these certificates are issued by the manufacturer to the importing agent (i.e., the product-licence holder in the importing country), but they must be made available at the request of – or in the course of any inspection made on behalf of – the competent national authority.

4. Issuing a certificate

4.1 The certifying authority is responsible for assuring the authenticity of the certified data. Certificates should not bear the WHO emblem, but a statement should always be included to confirm whether or not the document is issued in the format recommended by WHO.

4.2 When the applicant is the manufacturer of the finished dosage form, the certifying authority should satisfy itself, before attesting compliance with GMP, that the applicant:

(a) applies identical standards to the production of *all* batches of pharmaceutical products manufactured within the facility, *including those destined exclusively for export;*
(b) consents, in the event of identification of a quality defect consonant with the criteria set out in section 5.1, to relevant inspection reports being released, in confidence, to the competent authority in the country of import, should the latter so require.

4.3 When the applicant is not the manufacturer of the finished dosage form, the certifying authority should similarly satisfy itself – in so far as it has authority to inspect the records and relevant activities of the applicant – that it has the applicant's consent to release relevant reports on the same basis as described in section 4.2 (b) above.

4.4 GMP as recommended by WHO assigns to the manufacturer of the finished dosage form responsibility for assuring the quality of active ingredients. National regulations may require that suppliers of active ingredients be identified in the product licence, but the competent authority may have no power to inspect them.

4.5 Notwithstanding this situation, a certifying authority may agree, on a discretionary and voluntary basis, and at the request of a manufacturer, to undertake an inspection of a manufacturer of active ingredients to satisfy specific requirements of a requesting authority. Alternatively, pending the development of specific guidelines for active pharmaceutical ingredients, the certifying authority may be able to attest that the manufacturer is an established supplier of the substance in question to manufacturers of finished dosage forms licensed for marketing under its jurisdiction.

4.6 Whenever a product is purchased through a broker or another intermediary, or when more than one set of premises has been involved in the manufacture and packaging of a product, the certifying authority should consider whether it has received sufficient information to satisfy itself that those aspects of the manufacture of the product for which the applicant is not directly responsible have been undertaken in compliance with GMP as recommended by WHO.

4.7 The certifying authority should officially stamp and date all copies of product information submitted to it in support of an application for a certificate. Every effort should be made to ensure that certificates and all annexed documentation are consonant with the version of the product licence operative on the date of issue.

4.8 Any additional attachment to a certificate submitted by the applicant, such as price lists of products for which bids are offered, should be clearly identified as not forming part of the attestation made by the certifying authority.

4.9 To avert potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous, and to enable the certifying authority to maintain comprehensive records of countries to which specific products have been exported, each certificate should identify the importing country and be stamped on each page with the official seal of the certifying authority. An identical copy, clearly marked as duplicate, should be forwarded by the certifying authority on demand direct to the authority in the importing country.

5. Notifying and investigating a quality defect

5.1 Each certifying authority undertakes to institute inquiries into any quality defect reported in a product exported in accordance with the provisions of the Scheme, on the understanding that:

- the complaint is transmitted, together with the relevant facts, through the competent authority in the importing country;
- the complaint is considered to be of a serious nature by the latter authority; and
- the defect, if it appeared after delivery of the product into the importing country, is not attributable to local conditions.

5.2 In the case of obvious doubt, a participating national authority may request WHO to assist in identifying an independent quality control laboratory to carry out tests for the purposes of quality control.

5.3 Each certifying authority undertakes to inform WHO and, as far as is possible, all competent national authorities, of any serious hazard newly associated with a product exported under the provisions of the Scheme or of any criminal abuse of the Scheme directed, in particular, to the export of falsely labelled, spurious, counterfeited or substandard pharmaceutical products. On receipt of such notification, WHO will transmit the message immediately to the competent national authority in each Member State.

5.4 WHO stands prepared to offer advice should difficulty arise in implementing any aspect of the Scheme or in resolving a complaint, but it cannot be a party to any resulting litigation or arbitration.

References

1. Quality control of drugs. In: *Twenty-second World Health Assembly, Boston, Massachusetts, 8–25 July 1969. Part I: Resolutions and decisions, annexes.* Geneva, World Health Organization, 1969: 99–105 (Official Records of the World Health Organization, No. 176).
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. Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *Twenty-eighth World Health Assembly, Geneva, 13–30 May 1975. Part I: Resolutions and decisions, annexes.* Geneva, World Health Organization, 1975: 94–95 (Official Records of the World Health Organization, No. 226).
4. 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).

Appendix 1

Model Certificate of a Pharmaceutical Product

No. of Certificate.....

Certificate of a Pharmaceutical Product[1]

Exporting (certifying) country:
Importing (requesting) country:

Proprietary name (if applicable) and dosage form:
Active ingredient(s)[2] and amount(s) per unit dose:[3]

1. Is this product **licensed** to be placed on the market for use in the exporting country?[4] If yes, complete **box A.** If no, complete **box B.**

A

Product-licence holder:

Status of licence holder:[5] a ☐ b ☐ c ☐ d ☐

Number of product licence[6] and date of issue:

Is an approved technical summary appended?[7] yes ☐ no ☐

Is the attached product information complete and consonant with the licence?

yes ☐ no ☐ not provided ☐

Applicant for certificate **if different** from the licence holder:[8]

B

Applicant for certificate:

Status of applicant:[5] a ☐ b ☐ c ☐ d ☐

Why is authorization lacking?

not required ☐ not requested ☐ under consideration ☐ refused ☐

Remarks:[9]

2. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? yes ☐ no ☐ If no, proceed to question 3

Periodicity of routine inspections (years):

Has the manufacture of this type of dosage form been inspected? yes ☐ no ☐

Do the facilities and operations conform to GMP as recommended by the World Health Organization?[10] yes ☐ no ☐

3. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party?[11]

yes ☐ no ☐ If no, explain:

Address of certifying authority:

Telephone/fax numbers:

Name of authorized person:
Signature:
Stamp and date:

This certificate conforms to the format recommended by the World Health Organization *(General instructions and explanatory notes overleaf)*

General instructions

Please refer to the guidelines for further information on how to complete this form and on the implementation of the Scheme.

Forms should be completed using a typewriter to ensure legibility.

A cross should be placed in boxes as appropriate to indicate which options apply.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

[1] This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

[2] Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.

[3] A qualitative listing of other ingredients contained in the dosage form should be appended.

[4] When applicable, append details of any restriction applied to the sale, distribution, or administration of the product that is entered on the product licence.

[5] Specify whether the person responsible for placing the product on the market:
(a) manufactures the active ingredients and the finished dosage form;
(b) manufactures the finished dosage form;
(c) packages and/or labels a finished dosage form manufactured by an independent company; or
(d) is involved in none of the above.

[6] Indicate, when applicable, if the licence is provisional, pending technical review.

[7] This refers to the document, prepared by certain national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

[8] In this circumstance, permission for issuance of the certificate is required from the product-licence holder.

[9] Please indicate the reason the applicant has provided for not requesting registration:
(a) the product has been developed exclusively for the treatment of conditions — particularly tropical diseases — not endemic in the country of export;
(b) the product has been reformulated with a view to improving its stability under tropical conditions;
(c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;
(d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient;
(e) any other reason, please specify.

[10] The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those adopted by the Twenty-eighth World Health Assembly in its resolution WHA28.65 (see WHO Official Records, No. 226, 1975, Annex 12, Part 1). Proposals for the amendment of these requirements are included in the Thirty-second Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 822, 1992, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).

[11] This section is to be completed when the product-licence holder or applicant conforms to status (c) or (d) as described in note 5 above. It is of particular importance when foreign contractors are involved in the manufacture of the product.In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and to indicate the extent and nature of any controls exercised over each of these parties.

Appendix 2
Model Statement of Licensing Status of Pharmaceutical Product(s)

No. of statement.....

Exporting (certifying) country:
Importing (requesting) country:

Statement of Licensing Status of Pharmaceutical Product(s)[1]

This statement indicates **only** whether or not the following products are licensed to be placed on the market for use in the exporting country.
Applicant (name/address):

Proprietary name (if applicable)	Dosage form	Active ingredient(s)[2] and amount(s) per unit dose	Product-licence no. & date of issue[3]

The certifying authority undertakes to provide, at the request of the applicant (and, if different, the product-licence holder), a separate and complete Certificate of a Pharmaceutical Product in the format recommended by WHO, for each of the products listed above.

Address of certifying authority:

Telephone/fax numbers:

Name of authorized person:
Signature:
Stamp and date:

This certificate conforms to the format recommended by the World Health Organization *(General instructions and explanatory notes overleaf)*

General instructions

Please refer to the guidelines for further information on how to complete this form and on the implementation of the Scheme.
Forms should be completed using a typewriter to ensure legibility.
Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

[1] This statement is intended for use by importing agents who are required to screen bids made in response to an international tender and should be requested by the agent as a condition of bidding.

[2] Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.

[3] If no product licence has been granted, enter "not required", "not requested", "under consideration", or "refused" as appropriate.

Appendix 3
Model Batch Certificate of a Pharmaceutical Product

No. of Certificate..... Importing (requesting) country:

Manufacturer's/Official[1] Batch Certificate of a Pharmaceutical Product

Proprietary name (if applicable) and dosage form:
Active ingredient(s)[2] and amount(s) per unit dose:

Details of product licence and product certificate issued in the exporting country

Product-licence holder: Product-licence number: Date of issue:

Product licence issued by: Product-certificate number:[3]

Batch number: Date of manufacture: Shelf-life (years):

Contents of container: Nature of secondary container: Nature of primary container/wrapping:

Specific storage conditions recommended for the product: Temperature range:

Quality analysis

What specifications apply to this dosage form? Either specify the pharmacopoeia or append the specifications.

Does the batch comply in all particulars with the above specifications? yes ☐ no ☐

Append certificate of analysis.[4]

It is hereby certified that the above declarations are correct and that results of the analyses and assays on which they are based will be provided on request to the competent authorities in both the importing and the exporting countries.

Name and address of authorized person: Signature of authorized person:
Stamp:

Telephone/fax numbers: Date:

This certificate conforms to the format recommended by the World Health Organization *(General instructions and explanatory notes overleaf)*

General instructions

Please refer to the guidelines for further information on how to complete this form and on the implementation of the Scheme.

Forms should be completed using a typewriter to ensure legibility.

A cross should be placed in boxes as appropriate to indicate which options apply.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

Certification of individual batches of a pharmaceutical product is only undertaken exceptionally by the competent authority of the exporting country. Even then, it is rarely applied other than to vaccines and biologicals. For other products, the responsibility for any request to provide batch certificates rests with the product-licence holder in the exporting country. The responsibility to forward certificates to the competent authority in the importing country is most conveniently assigned to the importing agent.

Any inquiries or complaints regarding a batch certificate should always be addressed to the competent authority in the exporting country. A copy should be sent to the product-licence holder.

[1] Strike out whichever does not apply.

[2] Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.

[3] This refers to the Certificate of a Pharmaceutical Product as recommended by the World Health Organization.

[4] Identify and explain any discrepancies from specifications.

Annex 4

Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology

1. Introduction

These guidelines are concerned with the quality assurance of pharmaceutical and biological products made using recombinant DNA (rDNA) techniques and intended for use in humans.

Individual countries may wish to use this document to develop their own national guidelines or requirements for rDNA-derived products. It is not intended to apply to the control of genetically modified live organisms designed to be used directly in humans, e.g., live vaccines.

The purpose of the document is to indicate:

- appropriate methods for the manufacture and testing of rDNA-derived products; and
- information specific to rDNA products that should be included in submissions by manufacturers to national control authorities in support of applications for the authorization of clinical trials and marketing.

It is recognized that rDNA technology is a rapidly evolving field and that it is important that a flexible approach to the control of these products be adopted so that requirements can be modified in the light of experience of production and use, and the further development of new technologies. The guidelines presented here therefore supersede those published in 1983 (*1*), and the intention is to provide an updated and scientifically sound basis for the manufacture and control of medicinal products produced by new biotechnologies.

2. General considerations

Advances in molecular genetics and nucleic acid chemistry now enable genes coding for natural biologically active proteins to be identified, analysed in fine detail, transferred from one organism to another and expressed under controlled conditions so as to synthesize efficiently the polypeptides for which they code. A gene is characterized by a specific nucleotide sequence in each strand of the double-stranded DNA molecule. When the strands are separated, each forms a template for the synthesis of a complementary copy, thus providing a mechanism for the faithful reproduction of genes while at the same time conserving the linear sequence of the four mononucleotide building blocks. The process of decoding this information and synthesizing the gene product takes place in the following two stages: (i) transcription of the DNA coding strand in the form of messenger RNA (mRNA); and (ii) translation of the information carried by the mRNA molecule into a polypeptide. Genes coding for modified products possessing enhanced biological activity and/or fewer undesirable characteristics, as well as for entirely novel substances, can now be constructed.

A naturally occurring gene or a synthetically derived nucleotide sequence that codes for a specific product can be propagated by inserting the DNA into a suitable vector. For this purpose, highly specific restriction endonuclease enzymes (which cleave the vector DNA at predetermined sites) and ligases (which join the gene insert to the vector) are used, after which the vector is introduced into a suitable host organism. Individual clones that carry the desired gene can then be selected and grown in mass culture so as to ensure the efficient expression of the desired gene product. The factors affecting the expression of foreign genes introduced into a new host are, however, complex, and the efficient, controlled and faithful expression of stable, cloned DNA sequences is an important objective of current research.

Many vectors in use at present are bacterial plasmids and much gene cloning has been carried out in prokaryotes. However, other vector-host cell systems involving eukaryotes, including yeasts or continuously growing (transformed) cell lines of mammalian or insect origin, have been developed and are, in some cases, already used for production. The use of animal cells as hosts is considered by some to offer distinct advantages as compared with bacterial systems. They can, for example, effect modifications, such as the addition of carbohydrate groups, which may take place on mammalian proteins. Correct processing is also more likely and secretion of the product into the culture medium avoids the need to disrupt the cells and thus reduces potential contamination with host-cell proteins. On the other hand, the use of animal cells as hosts does raise specific safety issues (see below).

Certain factors may compromise the quality, safety and efficacy of rDNA-derived products and these need special attention, as indicated in the following paragraphs.

Products from naturally occurring genes expressed in foreign hosts may differ structurally, biologically or immunologically from their natural counterparts. Such differences can arise either at the genetic, post-transcriptional or post-translational level, or during production and/or purification.

In addition, rDNA-derived products may contain potentially hazardous contaminants not normally present in their equivalents prepared by conventional means and which the purification process must be capable of eliminating. Examples include endotoxins in products expressed in bacterial cells and contaminating cellular DNA and viruses in those derived from animal cells. Contamination with nucleic acid from transformed mammalian cells is a particular concern because of the possible presence of potentially oncogenic DNA. The choice of manufacturing procedure will, of course, influence the nature and range of possible contaminants.

The "scaling up" of laboratory techniques into processes suitable for large-scale production may significantly affect the quality of the product and thus have major implications for control and testing. Unintended variability in the culture during production may lead to changes that favour the expression of other genes in the host/vector system or that cause alterations in the polypeptide product. Such variations might result in decreased yield of the product and/or quantitative and qualitative differences in the impurities present. Similar considerations apply to the use of continuous culture production. Consequently, procedures to ensure the consistency both of production conditions and of the final product are essential.

3. Scope of guidelines

The guidelines cover the following three main areas:

1. Control of starting materials, including baseline data both on the host cell and on the source, nature and sequence of the gene used in production.
2. Control of the manufacturing process.
3. Control of the final product.

In this respect, rDNA products are considered to be similar to biologicals produced by traditional methods, such as bacterial and viral vaccines, where adequate control of the starting materials and manufacturing procedure is just as necessary as that of the product. The guidelines therefore place considerable emphasis on "in-process" controls for ensuring the safety and effectiveness of the product, as well as on the comprehensive characterization of the final product itself. The validation of certain aspects of the manufacturing process, such as the ability of the purification procedure to remove unwanted materials, e.g., DNA, is also considered to be essential.

Requirements relating to establishments in which biological products are manufactured (e.g., the revised Requirements for Biological Substances No. 1, (*2*)) apply to rDNA-derived products, as do the general requirements for the quality control of biological products. Appropriate attention therefore needs to be given to the quality of all reagents used in production, including components of fermentation media. If animal-derived additives are used (e.g., calf serum), they should be shown to be free from adventitious agents. It is undesirable to use in production any agent known to provoke sensitivity reactions in certain individuals, such as penicillin or other β-lactam antibiotics. Many of the general requirements for the quality control of biological products, such as tests for potency, abnormal toxicity, pyrogenicity, stability and sterility, also apply to products made by rDNA techniques.

While the guidelines set out below should be considered as generally applicable, individual products may present particular quality control problems. The production and quality control of each product must therefore be given careful individual consideration, any special features being taken fully into account. Furthermore, the guidelines for a product must reflect its intended clinical use. Thus, a preparation that is to be administered repeatedly over a protracted period of time, or in large doses, is likely to need careful testing for traces of antigenic contaminants. Different criteria might justifiably apply, however, to a product to be used only once but in a life-threatening condition.

When the term "bulk product" is used in these guidelines, it refers to the substance in question following purification but before final formulation.

4. Control of source materials

4.1 *Expression vector and host cell*

A description of the host cell, its source and history, and of the expression vector used in production should be given. This should include details of the origin and identity of the gene being cloned as well as the construction, genetics and structure of the expression vector. An explanation of the source and function of component parts of the vector, such as the origins of replication, promoters or antibiotic-resistance markers, should be provided, as should a restriction-enzyme digestion map indicating at least those sites used in construction.

Details of the method by which the vector is introduced into the host cell and the state of the vector within the cell, i.e., whether integrated or extrachromosomal, and copy number, should be provided. The genetic stability of the host-vector combination should be documented.

4.2 *Sequence of cloned gene*

The nucleotide sequence of the gene insert and of the flanking control regions of the expression vector should be indicated. All relevant expressed sequences should be clearly delineated.

4.3 *Expression*

Measures used to promote and control the expression of the cloned gene in the host cell during production should be described in detail.

5. Control of production

5.1 *Manufacturer's working cell bank*

The production of a rDNA product should be based on a seed lot system involving a manufacturer's working cell bank derived from the master seed lot. A host cell containing the expression vector should be cloned and used to establish a master seed lot. During the establishment of the seed, no other cell lines should be handled simultaneously in the same laboratory suite or by the same persons.

Full information should be provided on the origin, form, storage and life expectancy at the anticipated rate of use of seed material. Evidence for the stability of the host-vector expression system in the seed stock under storage and recovery conditions should also be provided. New seed lots should be fully characterized and acceptance criteria established.

Where higher eukaryotic cells are used for production, distinguishing cell markers, such as specific isoenzymes or immunological features, are useful in establishing the identity of the seed. Information on the tumorigenicity of continuous cell lines should be obtained and reported. Where microbial cultures are used, specific phenotypic features that can form a basis for identification should be described.

The DNA sequence of the cloned gene should normally be confirmed at the stage of the master seed lot. However, in certain cases, e.g., where multiple copies of the gene are inserted into the genome of a continuous cell line, it may be inappropriate to sequence the cloned gene at this stage. In such circumstances, Southern blot analysis of the total cellular DNA, Northern blot analysis of transcripts that contain the product sequence, or sequence analysis of product-related mRNA may be informative, and particular attention should be paid to the characterization of the final product.

Evidence that the seed lot is free from infective bacterial, mycoplasmal, fungal, viral and, where appropriate, potentially oncogenic adventitious agents should be provided. Special attention should be given to viruses that commonly contaminate the animal species from which cell lines are derived. Seed lots should preferably be free from all adventitious agents. However, certain cell lines contain endogenous viruses, e.g., retroviruses. Tests capable of detecting such organisms should be carried out under a variety of conditions known to cause their induction, and the results reported. Specific contaminants identified as endogenous agents in the master seed lot, or as part of the vector, should be shown to be inactivated and/or removed by the purification procedures used in production.

5.2 *Production at finite passage*

Procedures and materials used both for cell growth and for the induction of the product should be described in detail. For each production run, data on the extent and nature of any microbial contamination of the culture vessels immediately before harvesting should be provided. Acceptable limits for such contamination should be set and the sensitivity of the methods used to detect it indicated.

Data on the consistency of fermentation conditions and culture growth, and on the maintenance of product yield should be presented. Criteria for the rejection of culture lots should be established. The maximum number of cell doublings or passage levels to be permitted during production should be specified, based on information on the stability of the host-cell/vector system on serial subculture up to and beyond the level used in production.

Host-cell/vector characteristics at the end of production cycles should be monitored, for which purpose detailed information on plasmid copy number and degree of retention of the expression vector within the host cell may be of value, as may restriction-enzyme mapping of the vector containing the gene insert. The nucleotide sequence of the insert encoding the rDNA product should be determined, where appropriate (see section 5.1), at least once after full-scale culture for each master seed lot. If the vector is present in multiple copies integrated into the host-cell genome, confirming the rDNA sequence directly may be difficult. In such cases, the isolation and determination of the nucleotide sequence of the product-related mRNA, Northern blot analysis of product-related transcripts or Southern blot analysis of total DNA should be considered.

5.3 *Continuous culture production*

As recommended in section 5.2, all procedures and materials used for cell culture and induction of the product should be described in detail. In addition, particular consideration should be given to the procedures used in production control. Monitoring is necessary throughout the life of the culture, although the frequency and type of monitoring required depend on the nature of both the production system and the product.

The molecular integrity of the gene being expressed and the phenotypic and genotypic characteristics of the host cell after long-term cultivation should be established. Evidence should also be produced to show that variations in yield do not exceed the specified limits. The acceptance of harvests for further processing should be clearly linked to the monitoring schedule in use, and a clear definition of a "batch" of product for further processing will be required. Criteria for the rejection of harvests or termination of the culture should also be established. Regular tests for microbial contamination should be performed as appropriate to the harvesting strategy.

The maximum period of continuous culture should be specified, based on

information on the stability of the system and consistency of the product during and after this period. In long-term continuous culture, the cell line and product should be fully re-evaluated at intervals determined by information on the stability of the host-vector system and the characteristics of the product.

5.4 *Purification*

The methods used for harvesting, extraction and purification should be described in detail. Special attention should be given to the elimination of viruses, nucleic acid, and undesirable antigenic materials.

In procedures involving affinity chromatography using biological substances, such as monoclonal antibodies, appropriate measures should be taken to ensure that these substances, or any other potential contaminants arising from their use, such as adventitious viruses, do not compromise the safety of the final product.

The ability of the purification procedure to remove unwanted product-related or host-cell-derived proteins, nucleic acid, carbohydrate, viruses or other impurities, including media-derived components and undesirable chemicals introduced by the purification process itself, should be investigated thoroughly, as should the reproducibility of the process. Data from validation studies on the purification procedures may be required to demonstrate clearance of DNA or viruses, both at each purification step and overall. In such pilot-scale studies, tests should be carried out with a carefully selected group of viruses exhibiting a range of physicochemical characteristics representative of potential contaminants, or with radiolabelled DNA, deliberately added to the crude preparation ("spiking"). The results will indicate the extent to which these contaminants can theoretically be removed during purification. Any virus-inactivation process used should be shown to be effective and not to compromise the quality of the product.

6. Characterization of bulk product

The identity, purity, potency and stability of the bulk product should be established. The type of testing necessary and the degree of purity expected will depend on several factors, including the nature and intended use of the product, the method of production and purification, and experience with the production of several batches of the product.

6.1 *Characterization of purified active substance*

Rigorous characterization of the active substance by chemical, physical and biological methods will be essential. Particular attention should be given to using a wide range of analytical techniques exploiting different physicochemical properties of the molecule (size, charge, isoelectric point, amino-acid composition and hydrophobicity). It may also be necessary to include suitable tests to establish that the product has the desired

conformation and state of aggregation. Techniques suitable for such purposes include polyacrylamide gel electrophoresis; isolectric focusing; size-exclusion, reversed-phase, ion-exchange, hydrophobic-interaction or affinity chromatography; peptide mapping; amino-acid analysis; light scattering; and ultraviolet spectroscopy. Circular dichroism and other spectroscopic techniques can also provide valuable information.

Where relevant and possible, the properties of the product should be compared with those of the naturally occurring molecule.

The product should be shown to possess the expected biological activity; this should be of the expected magnitude and the potency of the product in appropriate units should be determined. In addition, the determination of the specific activity (units of activity/weight of product) of highly purified material is of particular value.

Sufficient sequence information to characterize the product should be obtained. The degree of sequence verification required will depend on the scope of other characterization tests. For some purposes, partial sequence determination and peptide mapping may suffice; for others, full sequence determination may be necessary. Attention should be paid to the possible presence of N-terminal methionine, signal or leader sequences and other possible N- and C-terminal modifications (such as acetylation, amidation or partial degradation by exopeptidases). Other post-translational modifications, such as glycosylation, should be identified and adequately characterized. Special consideration should be given to the possibility that such modifications are likely to differ from those found in a natural counterpart and may influence the biological, pharmacological and immunological properties of the product.

6.2 *Purity*

Data should be provided on the contaminants present in the product, including estimates of their maximum levels. The degree of contamination considered acceptable and criteria for the rejection of a production batch should be specified.

It is important that the techniques used to demonstrate purity be based on as wide a range of physicochemical properties as possible. Attention should be given to tests for viral and nucleic acid contamination and for other unwanted materials of host or product origin, as well as materials that may have been added during the production or purification processes. Limits should be specified for all impurities detected, and these should be identified and characterized as appropriate.

Substances that are to be administered repeatedly or in large doses should be assayed for trace antigenic constituents and product-related impurities, such as aggregates or degradation products likely to contaminate the final product, and strict upper limits specified. Tests such as immunoblotting, radioimmunoassays and enzyme-linked immunosorbent assays using high-affinity antibodies raised against the product, host-cell lysates,

appropriate subcellular fractions and culture medium constituents can be used to detect contaminating antigens. Because the detection of antigens will be limited by the specificity and sensitivity of the antisera used, these immunoassays will complement, but not replace, other techniques, such as staining of gels used in sodium dodecyl sulfate/polyacrylamide gel electrophoresis. Patients given large or repeated doses of a product during clinical trials should be monitored for the production of antibodies both to contaminating antigens and to the product.

7. Routine control of final dosage form

It will be apparent that not all the tests described above need to be carried out on each batch of final dosage form. Some tests are required only to establish the validity or acceptability of a procedure, while others might be performed on a limited series of batches in order to establish consistency of production. Thus, a comprehensive analysis of the initial production batches should be undertaken to establish consistency with regard to identity, purity and potency; after the stability of the final dosage form has been established, a more limited series of tests may be appropriate, as outlined below.

7.1 *Consistency*

An acceptable number, e.g., five, successive batches of final dosage form should be characterized as fully as possible to determine consistency of composition. Any differences between one batch and another should be noted. The data obtained from such studies should be used as the basis for the product specification.

7.2 *Identity*

Each batch of final dosage form should be subjected to a selection of the tests used to characterize the purified active substance in order to confirm product identity. The specific tests that adequately characterize any particular product on a lot-to-lot basis, however, depend on both the nature of the product and the method of production. Depending on the scope of other identification tests, sequence verification of a number of amino acids at the N- and C-termini, or the use of other methods, such as peptide mapping, will be necessary.

7.3 *Purity*

The purity of each batch of final dosage form should be determined and be within specified limits. The analysis should include sensitive and reliable assays for DNA of host-cell origin (e.g., hybridization analysis of immobilized contaminating DNA, using appropriate probes) for each batch of product prepared from continuous lines of mammalian cells (transformed cell lines); strict upper limits should be specified for the DNA content of the product. Theoretical concerns regarding transforming DNA derived from the cell substrates can be minimized by the general

reduction in contaminating nucleic acid (*3*). DNA analyses should also be performed on each batch of product obtained from other eukaryotic cells, and limits specified for DNA content, until such time as further information on safety is obtained. Wherever appropriate from the point of view of the quality and safety of the product, tests for DNA of prokaryotic expression systems should be carried out.

For products to be administered for an extended period of time or in high doses, the residual cellular proteins should also be determined by an assay of appropriate sensitivity and strict upper limits specified.

7.4 *Potency*

The potency of each batch of the final dosage form should be established using, wherever possible, an appropriate national or international reference material calibrated in units of biological activity. In the absence of such preparations, an approved in-house reference preparation may be used for assay standardization.

When sufficient correlation studies between physicochemical or *in vitro* bioassays and *in vivo* biological assays have been carried out showing that estimates based on *in vitro* tests are sufficiently precise and accurate, the requirement for an *in vivo* bioassay may be relaxed.

8. Reference materials

The studies described in section 6 together with those in section 7 will contribute to a definitive specification for the product.

A suitable batch of the product, preferably one that has been clinically evaluated, should be fully characterized in terms of its chemical composition, purity and biological activity, including, where possible, full amino-acid sequencing, and retained for use as a chemical and biological reference material. Where appropriate, these properties should be compared with those of a highly purified preparation of the naturally occurring molecule.

9. Preclinical safety evaluation

The general aim of preclinical safety evaluation is to determine whether new medicinal products have the potential to cause unexpected and undesirable effects. However, classical safety or toxicological testing, as recommended for chemical drugs, may be of only limited relevance for rDNA-derived products. These pose particular problems in relation to toxicity testing in animals, and their safety evaluation will have to take a large number of factors into account. Thus, certain proteins, e.g. interferons, are highly species-specific, so that the human protein is much more pharmacologically active in humans than in any other animal species. Furthermore, the amino-acid sequences of human proteins will often differ significantly from those of their natural counterparts in other species, as will the carbohydrate groups. Thus human proteins frequently produce

immunological responses in foreign hosts which may ultimately modify their biological effects and may result in toxicity due to immune complex formation. Such toxicity would, of course, have little bearing on the safety of the product in the intended human host.

For these and other reasons, it is likely that a flexible approach will be necessary for the preclinical safety evaluation of rDNA-derived products. Although there can be no doubt that some safety testing will be required for most products, the range of tests that need to be carried out should be decided on a case-by-case basis, in consultation with the national control authority. A wide range of pharmacological, biochemical, immunological. toxicological and histopathological investigative techniques should be used, where appropriate, in the assessment of a product's effect, over an appropriate range of doses and during both acute and chronic exposure. However, the points made above concerning species-specificity and antibody formation should always be taken into consideration. Where studies are expected to last more than four weeks, the use of test species known to be low responders from the point of view of antibody production against the test substance should be considered.

References

1. Quality control of biologicals produced by recombinant DNA techniques — WHO Consultation. *Bulletin of the World Health Organization,* 1983, 61:897–911.
2. General Requirements for Manufacturing Establishments and Control Laboratories (Requirements for Biological Substances, No. 1). In: *Requirements for biological substances. Report of a WHO Expert Group.* Geneva, World Health Organization, 1966: 11–22 (WHO Technical Report Series, No. 323).
3. *Acceptability of cell substrates for production of biologicals.* Geneva, World Health Organization, 1987 (WHO Technical Report Series, No. 747).

Appendix

Explanations of terms

Bulk harvest: A homogeneous pool of individual harvests or lysates processed in a single manufacturing run.

Bulk product: The product following purification, but before final formulation. It is obtained from a bulk harvest, and is kept in a single container and used in the preparation of the final dosage form.

Continuous culture production: A system in which the number of passages or population doublings after production has been started is not restricted. Strict criteria for terminating production must be specified by the manufacturer.

Final dosage form: The finished formulated product; it may be freeze-dried and contain excipients, which should have been shown not to affect stability adversely.

Manufacturer's working cell bank: A homogeneous suspension of the seed material derived from the master seed bank(s) at a finite passage level, dispensed in aliquots into individual containers for storage. All containers are treated identically and, once removed from storage, are not returned to the seed stock.

Master seed: A homogeneous suspension of the original cells, already transformed by the expression vector containing the desired gene, dispensed in aliquots into individual containers for storage. All containers are treated identically during storage and once removed from it are not returned to the seed stock.

Plasmid: An autonomously replicating, circular, extrachromosomal DNA element. It usually carries a few genes, some of which confer resistance to various antibiotics; such resistance is often used to discriminate between organisms that contain the plasmid and those that do not.

Production at finite passage: A cultivation method involving a limited number of passages or population doublings which must not be exceeded during production.

Vector: A piece of DNA that can direct its own replication within a host cell and to which other DNA molecules can be attached and thus amplified. Many vectors are bacterial plasmids, but in other instances a vector may be integrated into the host-cell chromosome following its introduction into the cell and is maintained in this form during the growth and multiplication of the host organism.

Annex 5

Validation of analytical procedures used in the examination of pharmaceutical materials

1. What is analytical validation?

Analytical monitoring of a pharmaceutical product, or of specific ingredients within the product, is necessary to ensure its safety and efficacy throughout all phases of its shelf-life, including storage, distribution, and use. Ideally, this monitoring should be conducted in accordance with specifications elaborated and validated during product development. This ensures that the quality specifications are applicable to the pharmaceutical material used to establish the biological characteristics of the active substances as well as to the marketed dosage forms. When the biomedical evaluation of the product is completed, the acceptability of all subsequent batches will be judged solely on the basis of these specifications.

The principal purpose of analytical validation is to ensure that a selected analytical procedure will give reproducible and reliable results that are adequate for the intended purpose. It is thus necessary to define properly both the conditions in which the procedure is to be used and the purpose for which it is intended. These principles apply to all procedures described in a pharmacopoeia and to non-pharmacopoeial procedures used in a manufacturing company.

These guidelines apply to procedures used to examine chemical and physicochemical attributes, but many are equally applicable to microbiological and biological procedures.

2. Presentation of data on analytical procedures for product registration or pharmacopoeial monographs

Any data on analytical procedures presented in support of a specification proposed for a particular ingredient (drug substance or excipient) or dosage form should be provided under three main headings:

1. *Justification of the proposed test procedure in comparison with other possible approaches.* Where an unusual procedure is proposed, its scientific basis should also be discussed. Where the procedure is being proposed to replace an existing one, comparative data should be provided.
2. *Description of the procedure giving as much detail as is deemed necessary to allow properly trained workers to carry it out in a reliable manner.* The reagents required should be defined (either in detail or by reference to readily available published texts) and details concerning the availability of any reference substances required should be given. Where the procedure is based on the application of well established principles of analytical chemistry, it should not be necessary to provide formulae for

the calculation of results. Where, however, the method is complex, a full formula for the calculation of results should be included, with all terms defined.

3. *Validation data.* Each analytical performance characteristic that is applicable to the particular procedure defined (see section 4) should be discussed and supported by experimental data. Where the data presented for registration purposes rely on established pharmacopoeial methods, the need for supporting validation data may be considerably reduced, on the assumption that the pharmacopoeial procedures have already been properly validated. However, evidence that the pharmacopoeial procedure is applicable to the material under test may well be required, especially for dosage forms.

3. Characteristics of analytical procedures

The characteristics that may need to be specified for analytical procedures are listed below and defined (for the purposes of this annex), with an indication of how they may be determined.

Not all the characteristics are applicable to every test procedure or to every material. Much depends on the purpose for which the procedure is required. This aspect of validation is discussed in section 4.

Accuracy. The accuracy of the procedure is the closeness of the results obtained by the procedure to the true value. Accuracy may be determined by applying the procedure to samples of the material to be examined that have been prepared with quantitative accuracy. Wherever possible, these samples should contain all the components of the material, including the analyte. Samples in which the analyte has been incorporated in quantities some 10% above and below the expected range of values should also be prepared. Accuracy may also be determined by comparing the results with those obtained using an alternative procedure that has already been validated.

Precision. The precision of the procedure is the degree of agreement among individual test results. It is measured by the scatter of individual results from the mean and it is usually expressed as the standard deviation or as the coefficient of variation (relative standard deviation) when the complete procedure is applied repeatedly to separate, identical samples drawn from the same homogeneous batch of material.

Repeatability (within-laboratory variation). This is the precision of the procedure when repeated by the same analyst under the same set of conditions (same reagents, equipment, settings, and laboratory) and within a short interval of time. The repeatability of a procedure is assessed by carrying out complete, separate determinations on separate, identical samples of the same homogeneous batch of material and thus provides a measure of the precision of the procedure under normal operating conditions.

Reproducibility. This is the precision of the procedure when it is carried out under different conditions – usually in different laboratories – on separate, putatively identical samples taken from the same homogeneous batch of material. Comparisons of results obtained by different analysts, by the use of different equipment, or by carrying out the analysis at different times can also provide valuable information.

Robustness. Robustness, or ruggedness, is the ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions. It is a measure of the exent to which the results obtained from separate, putatively identical samples of the same homogeneous batch of material are influenced by changes in operational or environmental conditions but are consonant with the specifications laid down for the procedure.

Linearity and range. The linearity of an analytical procedure is its ability to produce results that are directly proportional to the concentration of analyte in the samples. The range of the procedure is an expression of the lowest and highest levels of analyte that have been demonstrated to be determinable with acceptable precision, accuracy, and linearity. These characteristics are determined by application of the procedure to a series of samples having analyte concentrations spanning the claimed range of the procedure. When the relationship between response and concentration is not linear, standardization may be provided by means of a calibration curve.

Selectivity. The selectivity or specificity of a procedure is its ability to measure the analyte in a manner that is free from interference from other components in the sample being examined (for example, impurities arising from manufacture or degradation or ingredients other than the analyte, whether these are pharmacologically active or inert). Selectivity (or lack of it) may be expressed in terms of the bias of the assay results obtained when the procedure is applied to the analyte in the presence of expected levels of other components, compared to the results obtained on the same analyte without added substances. When the other components are all known and available, selectivity may be determined by comparing the test results obtained on the analyte with and without the addition of the potentially interfering materials. When such components are either unidentified or unavailable, a measure of selectivity can often be obtained by determining the recovery of a standard addition of pure analyte to a material containing a constant level of the other components.

Sensitivity. Sensitivity is the capacity of the test procedure to record small variations in concentration. It is the slope of the calibration curve. A more general use of the term to encompass limit of detection and/or limit of quantitation should be avoided.

Limit of detection. The limit of detection is the lowest level of analyte that can be detected, but not necessarily determined in a quantitative fashion, using a specific method under the required experimental conditions. Such

a limit is usually expressed in terms of a concentration of analyte (for example, in micrograms per litre) in the sample. Where the final measurement is based on an instrumental reading, due account will need to be taken of the background response (the signal-to-noise characteristics of the responses observed).

Limit of quantitation. The limit of quantitation is the lowest concentration of analyte in a sample that may be determined with acceptable accuracy and precision when the required procedure is applied. It is measured by analysing samples containing diminishing known quantities of the analyte and determining the lowest level at which acceptable degrees of accuracy and precision are attainable. Where the final assessment is based on an instrumental reading, the magnitude of background response (the signal-to-noise ratio) may need to be assessed and taken into account. In many cases the limit of quantitation is approximately twice the limit of detection.

4. What analytical characteristics are applicable in particular cases?

Not all of the characteristics referred to in section 3 will need to be considered in all cases; those applicable should be identified on a case-by-case basis. As a guide, however, the following generalizations may assist.

Methods used for the examination of pharmaceutical materials may be broadly classified as follows:

- Class A: Tests designed to establish identity, whether of bulk drug substances or of a particular ingredient in a finished dosage form.
- Class B: Methods designed to detect and quantitate impurities in a bulk drug substance or finished dosage form.
- Class C: Methods used to determine quantitatively the concentration of a bulk drug substance or of a major ingredient in a finished dosage form.
- Class D: Methods used to assess the characteristics of finished dosage forms, such as dissolution profiles and content uniformity.

Table 1 offers guidelines to the characteristics that are relevant in each case. Notwithstanding these generalizations, there will clearly be occasions when certain characteristics marked as not being required may be necessary and vice versa. In addition, the purpose for which the submission is being made may have a bearing on the choice of characteristics and the extent to which they are specified. For example, although Classes B, C, and D are all referred to in Table 1 as requiring consideration of precision, the stringency applied may be different. For estimation of an impurity it may not be necessary to be as precise as for quantitaive assessment of a bulk drug substance. By the same token, a degree of bias may be acceptable in determining the accuracy of a test for uniformity of content (Class D) that would not be permissible for a quantitative assessment of the concentration of an ingredient in a finished

Table 1
Characteristics that should be considered for different types of analytical procedure

	Class A	Class B		Class C	Class D
		Quantitative tests	Limit tests		
Accuracy		X		X	X[a]
Precision		X		X	X
Robustness	X	X	X	X	X
Linearity and range		X		X	X
Selectivity	X	X	X	X	X
Limit of detection	X		X		
Limit of quantitation		X			

[a] A degree of bias may be allowed.

dosage form (Class C). Similarly, a test designed to establish the identity of a new drug entity for which no previous data have been lodged may need to be considerably more searching than tests designed to verify the identity of a long-established drug substance to be included in a pharmacopoeia.

A different emphasis may be required for pharmacopoeial as opposed to registration purposes. For example, robustness is a critical characteristic for pharmacopoeial methodology but may be less significant for a manufacturer's release specification.

Annex 6

List of available International Chemical Reference Substances[1]

International Chemical Reference Substances are established on the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of drugs published in *The international pharmacopoeia* or proposed in draft monographs.

Directions for use and the analytical data required for the tests specified in *The international pharmacopoeia* are given in the certificates enclosed with the substances when distributed. More detailed analytical reports on the substances may be obtained on request from the WHO Collaborating Centre for Chemical Reference Substances.

International Chemical Reference Substances may also be used in tests and assays not described in *The international pharmacopoeia.* However, the responsibility for assessing the suitability of the substances then rests with the user or with the pharmacopoeia commission or other authority that has prescribed their use.

It is generally recommended that the substances be stored protected from light and moisture and preferably at a temperature of about +5 °C. When special storage conditions are required, this is stated on the label or in the accompanying leaflet.

The stability of the International Chemical Reference Substances kept at the Collaborating Centre is monitored by regular re-examination, and materials that have deteriorated are replaced by new batches when necessary. Lists giving control numbers for the current batches are issued in the annual reports from the Centre and may be obtained on request.

Orders for International Chemical Reference Substances should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteksbolaget AB
Centrallaboratoriet
S-105 14 Stockholm
Sweden

Telex: 115 53 APOBOL S
Fax: 46 8 740 60 40

International Chemical Reference Substances are supplied only in the standard packages indicated in the following list.

[1] As updated at the thirty-second meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 10–15 December 1990.

Reference substance	*Package size*
aceclidine salicylate	100 mg
p-acetamidobenzalazine	100 mg
acetazolamide	100 mg
allopurinol	100 mg
2-amino-5-nitrothiazole	25 mg
3-aminopyrazole-4-carboxamide hemisulfate	100 mg
amitriptyline hydrochloride	100 mg
ampicillin (anhydrous)	200 mg
ampicillin sodium	200 mg
ampicillin trihydrate	200 mg
anhydrotetracycline hydrochloride	25 mg
atropine sulfate	100 mg
azathioprine	100 mg
bendazol hydrochloride	100 mg
benzobarbital	100 mg
benzylamine sulfate	100 mg
benzylpenicillin potassium	200 mg
benzylpenicillin sodium	200 mg
bephenium hydroxynaphthoate	100 mg
betamethasone	100 mg
betamethasone valerate	100 mg
betanidine sulfate	100 mg
bupivacaine hydrochloride	100 mg
caffeine	100 mg
carbamazepine	100 mg
carbenicillin monosodium	200 mg
chloramphenicol	200 mg
chloramphenicol palmitate	1 g
chloramphenicol palmitate (polymorph A)	200 mg
5-chloro-2-methylaminobenzophenone	100 mg
2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid	50 mg
chlorphenamine hydrogen maleate	100 mg
chlorpromazine hydrochloride	100 mg
chlortalidone	100 mg
chlortetracycline hydrochloride	200 mg
cimetidine	100 mg
clomifene citrate	100 mg
clomifene citrate *Z*-isomer (zuclomifene)	50 mg
cloxacillin sodium	200 mg
colecalciferol (vitamin D_3)	500 mg
cortisone acetate	100 mg
dapsone	100 mg
desoxycortone acetate	100 mg
dexamethasone	100 mg

Reference substance	*Package size*
dexamethasone acetate	100 mg
diazepam	100 mg
diazoxide	100 mg
dicloxacillin sodium	200 mg
dicolinium iodide	100 mg
dicoumarol	100 mg
diethylcarbamazine dihydrogen citrate	100 mg
digitoxin	100 mg
digoxin	100 mg
N,N'-di-(2,3-xylyl)anthranilamide	50 mg
emetine hydrochloride	100 mg
4-epianhydrotetracycline hydrochloride	25 mg
4-epitetracycline ammonium salt	25 mg
ergocalciferol (vitamin D_2)	500 mg
ergometrine hydrogen maleate	50 mg
ergotamine tartrate	50 mg
estradiol benzoate	100 mg
estrone	100 mg
etacrynic acid	100 mg
ethambutol hydrochloride	100 mg
ethinylestradiol	100 mg
ethisterone	100 mg
ethosuximide	100 mg
etocarlide	100 mg
flucytosine	100 mg
fluorouracil	100 mg
fluphenazine decanoate dihydrochloride	100 mg
fluphenazine enantate dihydrochloride	100 mg
fluphenazine hydrochloride	100 mg
folic acid	100 mg
3-formylrifamycin	200 mg
furosemide	100 mg
griseofulvin	200 mg
haloperidol	100 mg
hydrochlorothiazide	100 mg
hydrocortisone	100 mg
hydrocortisone acetate	100 mg
(-)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine	25 mg
ibuprofen	100 mg
imipramine hydrochloride	100 mg
indometacin	100 mg
o-iodohippuric acid	100 mg
isoniazid	100 mg

Reference substance	*Package size*
lanatoside C	100 mg
levodopa	100 mg
levothyroxine sodium	100 mg
lidocaine	100 mg
lidocaine hydrochloride	100 mg
mefenamic acid	100 mg
melting point reference substances (set of 13 substances with melting temperatures ranging from +69 °C to +263 °C)	13×4 g
metazide	100 mg
methaqualone	100 mg
methyldopa	100 mg
methyltestosterone	100 mg
meticillin sodium	200 mg
metronidazole	100mg
nafcillin sodium	200 mg
neostigmine metilsulfate	100 mg
nicotinamide	100 mg
nicotinic acid	100 mg
niridazole	200 mg
niridazole-chlorethylcarboxamide	25 mg
norethisterone	100 mg
norethisterone acetate	100 mg
ouabain	100 mg
oxacillin sodium	200 mg
oxytetracycline dihydrate	200 mg
oxytetracycline hydrochloride	200 mg
papaverine hydrochloride	100 mg
pheneticillin potassium	200 mg
phenoxymethylpenicillin	200 mg
phenoxymethylpenicillin calcium	200 mg
phenoxymethylpenicillin potassium	200 mg
phenytoin	100 mg
prednisolone	100 mg
prednisolone acetate	100mg
prednisone	100 mg
prednisone acetate	100 mg
procaine hydrochloride	100 mg
procarbazine hydrochloride	100 mg
progesterone	100 mg
propicillin potassium	200 mg
propranolol hydrochloride	100 mg
propylthiouracil	100 mg
pyridostigmine bromide	100 mg

Reference substance	*Package size*
reserpine	100 mg
riboflavin	250 mg
rifampicin quinone	200 mg
sodium cromoglicate	100 mg
sulfamethoxazole	100 mg
sulfamethoxypyridazine	100 mg
sulfanilamide	100 mg
testosterone propionate	100 mg
tetracycline hydrochloride	200 mg
thioacetazone	100 mg
4,4′-thiodianiline	50 mg
tolbutamide	100 mg
tolnaftate	100 mg
trimethadione	200 mg
trimethoprim	100 mg
trimethylguanidine sulfate	100 mg
tubocurarine chloride	100 mg
vitamin A acetate (solution) (retinol acetate)	5 capsules[1]
warfarin	100 mg

[1] Each containing about 9 mg in 250 mg of oil.

Annex 7

List of adopted International Infrared Reference Spectra

aceclidine salicylate
acetazolamide
allopurinol
amitriptyline hydrochloride
ampicillin trihydrate

benzylpenicillin potassium
biperiden
biperiden hydrochloride
bupivacaine hydrochloride

caffeine
chlorphenamine hydrogen maleate
clofazimine

dextromethorphan hydrobromide
diazepam
dicolinium iodide
dicoumarol
diethylcarbamazine dihydrogen citrate
diphenoxylate hydrochloride

erythromycin ethylsuccinate
etacrynic acid
ethambutol hydrochloride (in KCl)
ethionamide
ethosuximide

gallamine triethiodide

hydrochlorothiazide

ibuprofen
indometacin
isoniazid

lidocaine

metronidazole

nicotinamide
noscapine

phenytoin
protionamide
pyrimethamine

spironolactone
sulfadimidine
sulfamethoxypyridazine

trihexyphenidyl hydrochloride
trimethoprim

Annex 8

Study on the quality of selected drugs at the point of use in developing countries

Protocol

Background

Over the past 10 years, the supply and availability of pharmaceuticals in developing countries have increased significantly. At the same time, concern about the quality, stability and safety of drugs has become of paramount importance, especially in view of increasing numbers of reports of substandard and counterfeit drugs being found on the market in developing countries. In addition, the influence of extreme climatic and environmental conditions in several developing countries has not been sufficiently studied.

The desire of UNICEF to know more about these problems began a few years ago with a study on drug stability during international transport, with WHO collaboration.

To reinforce knowledge in this area and to provide better services to countries, a further evaluation of the quality of drugs as close as possible to the point of use has been called for by both UNICEF and WHO.

It must be emphasized that an exhaustive approach to this subject would require the consideration of too many variables and that operational and budget constraints impose a more limited scope. However, with these limitations a protocol has been developed and is presented here.

Objectives

1. To estimate the prevalence of substandard and degraded pharmaceutical products in selected health facilities and dispensing outlets in developing countries in Africa, Asia, and Latin America.
2. To use this information in the design of further studies, should they be indicated, and to assess the contribution of either inadequate formulation or inappropriate storage in the distribution chain to the process of degradation.
3. To validate quality control laboratories based in developing countries with a view to promoting their sustainability and further development.

Selection of drugs to be studied

The choice of substances will be determined by the following criteria:

- their importance in terms of public health;
- their potential to save, extend, or improve the quality of life;
- the extent of their use in primary health care;
- their known potential for degradation on storage.

Preparations containing the following drug substances will be studied:

- amoxicillin, oral forms;
- ampicillin, oral and injectable forms;
- benzylpenicillin, injectable forms;
- chloramphenicol, oral and injectable forms;
- chloroquine, oral and injectable forms;
- co-trimoxazole (sulfamethoxazole + trimethoprim), oral forms;
- mebendazole, oral forms;
- paracetamol, oral forms;
- quinine, oral and injectable forms.

In each location, branded and generic monocomponent products containing the above substances will be sampled. Where different batches of a given product are being used concurrently, representative samples will be taken from a maximum of three batches for each source of drug. (For details, see section on standard operating procedures, page 130.)

Collection of samples

Samples should be collected from central medical stores, hospitals, and community dispensaries. Sampling will involve both drugs supplied by UNICEF and drugs coming from other sources, including, if applicable, locally manufactured products.

The sampling procedures will be consonant with recommendations formulated at the thirty-first meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 790, 1990, Annex 2).

Written permission to take samples in accordance with the detailed protocol will be obtained from each interested competent authority. Responsibility for the collection of the samples will be assumed by UNICEF field staff acting with the authorization of the competent national authority.

Selection of countries

Countries invited to collaborate in the survey have been chosen from among those with health programmes supported by UNICEF or WHO, in which drug supply is a major component, and which are engaged in activities connected with the essential drugs programme or Bamako Initiative-type activities. Africa will have priority. The following countries have been contacted:

- in Africa: Benin, Guinea, Mozambique, Uganda, the United Republic of Tanzania
- in Asia: Bangladesh, Myanmar
- in the Americas: Guatemala, Peru.

If any of these countries cannot participate in the study, others will be approached. In any case, in the early stages of the study, it may not be possible for budgetary reasons to involve all the listed countries.

Since other countries present similar climatic and storage conditions to those chosen for the study, the final results could reasonably be applied to them as well.

UNICEF country offices will contact national authorities to implement this study, and a focal point will be selected in each country to act in liaison with UNICEF headquarters.

Selection of testing laboratories

Results of tests will be validated in two different laboratories. For this purpose laboratories in developing countries will be paired with laboratories in industrial countries. To date, the Universities of Bradford (England), Oslo (Norway), and Pavia (Italy) have offered to participate. WHO-sponsored laboratories in developing countries, including those in Bangkok, Harare, and Panama, will be invited to collaborate.

Preparation of the final report

The final report should include, in addition to the presentation and discussion of results, an introductory section providing a brief overview of the existing literature and a discussion of any preventive or remedial measures that may be indicated, and of the role of inspectors and quality control laboratories in an efficient surveillance system.

Standard operating procedures

Standard operating procedures must be developed to facilitate the work of investigators and to standardize the approach during sampling.

Once the national authorities have agreed to participate in the drug study, a UNICEF focal point will be designated in each country for carrying out the sampling, working together with government staff, both having appropriate expertise. The names of focal points should be communicated to the Essential Drugs Unit, UNICEF, New York, attention: Essential Drugs Adviser.

What to sample

The drug products to be collected are listed on page 129. With the exception of co-trimoxazole (sulfamethoxazole + trimethoprim), drug items with more than one active principle are excluded from this study. For each drug product, any available strength can be sampled.

Three different sources will be considered for each drug formulation:

- UNICEF-supplied drugs (imported from the Copenhagen warehouse);
- other imported drugs;
- locally manufactured drugs.

Where to sample

Drugs should be collected from one facility at each of three levels:

- *central level,* e.g., central medical stores, if functioning, or drug storage facilities operated by UNICEF or WHO;
- *hospital level,* e.g., regional, provincial, or district hospitals, the facility selected being representative of its category, and located at least 50 km from any central-level facility;
- *health centre or dispensary level,* the facility being at least 50 km from a central-level facility, provided that all drugs are in principle available.

Only one facility should be selected from each level.

How to sample

For each source of drugs (UNICEF-supplied, other imported, and locally manufactured drugs), up to three batches of a given dosage form should be sampled, preferably from different manufacturers. This process should be carried out at each of the three sampling levels (central, hospital, dispensary) to give a maximum of 27 (3×9) samples.

Sampling should reflect the most common source of the products. Neither expired drugs nor mislabelled drugs[1] should be collected. Drug products must still have six months of shelf-life remaining. It is preferable that samples should be taken from batches that have been stored for at least six months. Mislabelled drug products should be reported, and essential information provided.

The size of the sample to be collected varies according to the dosage form, as shown in Table 1. If the available quantity is insufficient, the sample should not be taken.

Whenever possible, samples should be forwarded to laboratories in their original containers with legible labels, leaflets (if applicable), and markings. When this is not possible, samples should be packed in containers obtained from the UNICEF country offices together with self-adhesive labels, and the following should be clearly marked on each label:

- generic name (International Nonproprietary Name)
- brand name (if branded)
- strength of unit (specify salts, esters, etc.)
- manufacturer's name
- batch number
- date of manufacture
- expiry date
- site of sampling
- date of sampling.

[1] The product is considered mislabelled when at least one of the following pieces of information is missing or illegible: name of manufacturer, batch number, strength, date of manufacture, and expiry date.

Table 1
Minimum quantity of drug products to be collected

	Central medical stores	Hospital	Health centre/ dispensary
amoxicillin, tablet	200	100	100
amoxicillin, capsule	200	100	100
amoxicillin, suspension	200 ml	100 ml	100 ml
ampicillin, tablet	200	100	100
ampicillin, capsule	200	100	100
ampicillin, suspension	200 ml	100 ml	100 ml
ampicillin, powder for injection	40 containers (vials)	20 containers (vials)	20 containers (vials)
benzylpenicillin, powder for injection	40 containers (vials)	20 containers (vials)	20 containers (vials)
chloramphenicol, tablet	200	100	100
chloramphenicol, capsule	200	100	100
chloramphenicol, suspension	200 ml	100 ml	100 ml
chloramphenicol, powder for injection	40 containers (vials)	20 containers (vials)	20 containers (vials)
chloroquine, tablet	200	100	100
chloroquine, syrup	200 ml	100 ml	100 ml
chloroquine, injection	40 containers (ampoules)	20 containers (ampoules)	20 containers (ampoules)
co-trimoxazole, tablet	400	200	200
co-trimoxazole, capsule	400	200	200
co-trimoxazole, suspension	400 ml	200 ml	200 ml
mebendazole, tablet	200	100	100
mebendazole, suspension	200 ml	100 ml	100 ml

	Central medical stores	Hospital	Health centre/ dispensary
paracetamol, tablet	200	100	100
paracetamol, capsule	200	100	100
paracetamol, suspension	200 ml	100 ml	100 ml
quinine, tablet	200	100	100
quinine, injection	40 containers (ampoules)	20 containers (ampoules)	20 containers (ampoules)

When the original container cannot be used, capsules, tablets, and suspensions should be packed in plastic containers. Cotton wool should be used to fill any residual space in containers of capsules and tablets. Appropriate packaging materials should also be provided to protect glass containers.

All sampling operations should be carried out with care. Investigators should have clean hands before manipulating products. Furthermore, they should carry with them clean tools, such as knives, scissors, brushes (to remove dust before opening containers), and funnels (for extracting syrups and suspensions from large-volume containers).[1]

The investigators acting as focal points should fill out the sample description form. The UNICEF country office should keep a copy of each completed form.

If the samples have to be purchased, the UNICEF country offices will advance the funds needed. On request, the country offices will be reimbursed by UNICEF. As a guide for the reimbursements, the UNICEF price list should be consulted.

How and where to send drug samples

Drugs will be dispatched by UNICEF to the responsible person in three different consignments according to the following scheme:

(a) All dosage forms of amoxicillin, ampicillin, and benzylpenicillin will be sent to:

Department of Pharmaceutical Chemistry,
School of Pharmacy,
University of Bradford,
Bradford, West Yorkshire BD7 1DP, England.

[1] Large-volume containers (more than 500 ml) should be well shaken before decanting to ensure uniformity of dosage.

(b) All dosage forms of chloramphenicol, co-trimoxazole, and paracetamol will be sent to:

Department of Pharmaceutical Chemistry,
Faculty of Pharmacy,
University of Pavia,
Via Taramelli 12,
27100 Pavia, Italy.

(c) All dosage forms of chloroquine, quinine, and mebendazole will be sent to:

Department of Pharmaceutics,
Faculty of Science,
P.O. Box 1068,
University of Oslo,
0316 Oslo 3, Norway.

Once consignments have been properly labelled with the address of the testing laboratory (preprinted labels will be provided), samples for Pavia should be sent by regular courier pouch to UNICEF Florence, and samples for Bradford and Oslo to UNICEF Copenhagen.

These UNICEF offices will ensure the conveyance of the consignments by the fastest route to the corresponding institution.