

**I
N
T
E
R
A
G
E
N
C
Y
G
U
I
D
E
L
I
N
E
S**

**A MODEL QUALITY ASSURANCE
SYSTEM FOR PROCUREMENT
AGENCIES**



A MODEL QUALITY ASSURANCE SYSTEM FOR PROCUREMENT AGENCIES

Recommendations for quality assurance systems
focusing on prequalification of products and manufacturers,
purchasing, storage and distribution of pharmaceutical products

WORLD HEALTH ORGANIZATION
UNITED NATIONS CHILDREN'S FUND
UNITED NATIONS DEVELOPMENT PROGRAMME
UNITED NATIONS POPULATION FUND
WORLD BANK

Acknowledgements

This document was previously published as Annex 6 of the 40th Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series No. 937, Geneva, World Health Organization, 2006). WHO is grateful to the Committee members and to all of those acknowledged in that Technical Report.

© World Health Organization 2007

All rights reserved. Publications of the World Health Organization can be obtained from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int). Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to WHO Press, at the above address (fax: +41 22 791 4806; e-mail: permissions@who.int).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This publication contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

Contents

Introduction	5
Glossary	9
Module I. General requirements for procurement agencies	15
Introduction	15
I.1 Physical resources.....	15
I.1.1 Premises	15
I.1.2 Equipment	16
I.1.3 Materials and consumables.....	17
I.1.4 Financial systems.....	17
I.1.5 Human resources.....	18
I.2 Documentation of policies and standards.....	19
I.2.1 Quality manual	20
I.2.2 Standard operating procedures	20
I.2.3 Change control policy	22
I.2.4 Code of conduct.....	22
I.2.5 Guidelines on conflict of interest.....	23
I.2.6 List of prequalified products and manufacturers	23
I.2.7 Maintenance of records	24
Module II. Prequalification	25
Introduction	25
II.1 Principles for prequalification	25
II.1.1 WHO Model List of Essential Medicines	26
II.2 Standards for prequalification	26
II.3 Key persons and responsibilities	26
II.3.1 Staff responsible for prequalification	26
II.3.2 Staff responsible for evaluation of product information	27
II.3.3 Staff responsible for inspection of manufacturing sites.....	27
II.4 Key steps in prequalification	28
II.4.1 Step 1: solicit and receive expressions of interest	28
II.4.2 Step 2: receive product information.....	32

II.4.3	Step 3: screen product information.....	33
II.4.4	Step 4: evaluate product information.....	33
II.4.5	Step 5: plan, prepare and perform inspections	35
II.4.6	Step 6: finalize assessment process and update prequalification list	38
II.5	Requalification and monitoring	40
II.6	Monitoring of complaints.....	40
II.7	Cost recovery	40
 Module III. Purchasing.....		41
Introduction		41
III.1	Strategies for health systems.....	41
III.2	Procurement methods.....	42
III.2.1	Restricted tender	43
III.2.2	Competitive negotiation.....	43
III.2.3	Direct procurement.....	43
III.2.4	Open tender.....	43
III.3	Quality assurance in purchasing.....	43
III.4	Key activities in purchasing.....	44
III.4.1	Product selection and specification	44
III.4.2	Product quantification.....	44
III.4.3	Selection of suppliers.....	45
III.4.4	Adjudication of tenders	45
III.5	Organization and responsibilities	46
III.5.1	Procurement agency structure	46
III.5.2	Responsibilities.....	47
III.6	Monitoring of performance of prequalified manufacturers	48
III.7	Patents	48
III.8	Donations	49
 Module IV. Receipt and storage of purchased products.....		50
Introduction		50
IV.1	Pre-shipment quality control.....	50
IV.2	Receipt of stock	50
IV.3	Post-procurement quality control.....	51

IV.3.1 Sampling.....	51
IV.3.2 Rejected materials.....	51
IV.4 Storage of materials and products.....	52
IV.4.1 Staff.....	52
IV.4.2 Storage areas.....	52
IV.4.3 Storage conditions.....	52
IV.4.4 Labelling and containers.....	53
IV.4.5 Miscellaneous and hazardous materials.....	54
IV.4.6 Stock control.....	54
IV.4.7 Documentation: written instructions and records.....	55
Module V. Distribution.....	56
Introduction	56
V.1 Transport conditions.....	56
V.2 Cold chain	56
V.3 Temperature monitoring and records	56
V.4 Delivery order.....	56
V.5 Dispatch procedures and policies	57
V.6 Dispatch containers	57
V.7 Dispatch records	57
V.8 Traceability	57
V.9 Port of entry	57
V.10 Packaging of products and materials	57
Module VI. Reassessment.....	58
Introduction	58
VI.1 Re-evaluation of manufacturers.....	58
VI.2 Re-evaluation of products	58
VI.3 Monitoring of contracted-out services.....	59
VI.3.1 Storage and distribution	59
VI.3.2 Quality control laboratories.....	60
VI.3.3 Contract research organizations.....	60
Conclusion	60
References	62

Appendix 1 – Example of a code of conduct.....	65
Appendix 2 – Example of a guideline on confidentiality.....	71
Appendix 3 – Example of a guideline on conflict of interest	72
Appendix 4 – Example of a standard operating procedure (SOP) for writing an SOP	78
Appendix 5 – Example of an invitation for expression of interest.....	83
Appendix 6 – Pharmaceutical product questionnaire.....	88
Appendix 7 – Example of a standard operating procedure for screening and assessing product information.....	93
Appendix 8 – Technical questionnaire for pharmaceutical manufacturers	106
Appendix 9 – Example of a standard operating procedure for planning of inspections	114
Appendix 10 – Example of a standard operating procedure for preparing for an inspection	120
Appendix 11 – Example of a standard operating procedure for performing an inspection	125
Appendix 12 – Example of a checklist for good manufacturing practices.....	131
Appendix 13 – Guidance on good manufacturing practices: inspection report	133
Appendix 14 – Good storage practice.....	134
Appendix 15 – Good trade and distribution practices.....	135
Appendix 16 – Quality system recommendations for pharmaceutical inspectorates.....	136

Introduction

The World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and many other organizations are involved in the procurement of pharmaceutical products. In particular, the supply of pharmaceutical products used in the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), malaria and tuberculosis has become a major concern at both the international and country levels. Commitments by the European Commission and G8 countries, among others, offer the potential for significant increases in funding for efforts to combat communicable diseases. Low-cost pharmaceutical products of assured quality have the greatest potential for maximizing the impact of these efforts.

The need for a model quality assurance system

Efforts to accelerate access to pharmaceutical products used in the treatment of HIV/AIDS through negotiation and generic competition have highlighted the importance of quality assurance for procurement of pharmaceutical products and diagnostics. Considerable sums of money are invested in procuring pharmaceutical products from various manufacturers in different countries. However, evaluation of product-specific data and information on quality is often lacking, and inspections at manufacturing sites are not routinely performed to a consistent standard. At present, some organizations involved in procurement of pharmaceutical products do have quality systems for the different activities in place. However, these systems vary greatly between organizations. Some procurement agencies request manufacturers to submit a checklist or questionnaire containing product information for assessment. In some cases, these checklists fail to address important aspects that should be evaluated as part of prequalification. Others use detailed questionnaires or request product dossiers for evaluation. Some procurement agencies contract inspectors to perform inspections at the place of manufacture, but the extent and quality of these inspections may vary according to the resources available. Moreover, mutual recognition and coordination of such inspections is an exception rather than the rule.

Without a quality assurance system, organizations risk sourcing substandard, counterfeit or contaminated pharmaceutical products, leading to complaints about products and product recalls, wastage of money and serious health risks to patients. Such problems affect the credibility of procurement agencies, cause financial losses and put patients' safety in danger.

Background

A preparatory study carried out by a team of experts emphasized the substantial differences between prequalification of vaccines and pharmaceuticals. A pilot project to study the feasibility of prequalifying manufacturers of essential pharmaceutical products for treating priority diseases was recommended. The accumulated experience of experts from UNICEF, the United Nations Population Fund (UNFPA), WHO and the World Bank has identified the necessary elements to ensure appropriate procedures for procurement.

WHO therefore undertook a project with the above-mentioned United Nations partners, which was supported in principle by the World Bank. The project focused on the prequalification of products and manufacturers of HIV and AIDS-related products, and the drafting of a model quality assurance system (hereafter referred to as the Model). This Model is intended to assist organizations purchasing pharmaceutical products, vaccines, or other health sector goods or which are otherwise involved in the prequalification, purchasing, storage and distribution of such products, hereafter referred to as procurement agencies, to procure safe, effective pharmaceuticals of suitable quality.

Goal and objectives

The long-term goal of these recommendations is the design and implementation of a uniform and harmonized system that will ensure procurement of pharmaceutical products of defined quality for supply to patients, based on a mutually recognized process of prequalification of products and manufacturers by means of product dossier evaluation and inspection of manufacturing sites. Such a process, as defined in the Glossary and described in Module II, will hereafter be referred to as prequalification.

Establishing, harmonizing and implementing a quality assurance system for prequalification, purchasing, storage and distribution of pharmaceuticals is a task of considerable magnitude, which should be undertaken in stages. The following objectives were identified:

- creation of a model quality assurance system (MQAS) to be adopted and implemented by procurement agencies;
- creation of guidelines to harmonize the evaluation of data and information on products as part of the prequalification procedure; and
- creation of unified standards for inspection of manufacturers and suppliers to assess compliance with good manufacturing practices (GMP).

Quality assurance in procurement

Quality assurance is a wide-ranging concept which covers all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made to ensure that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates several factors and it is an integral part of all key activities in procurement.

The implementation of a quality assurance system in procurement, including systems for prequalification, storage and distribution, may affect costs. However, the benefits of ensuring quality outweigh the cost investment because they reduce the possible losses caused by the purchase and supply of substandard products.

Prequalification of products and manufacturers, purchasing, storage and distribution are complex processes that may involve many offices, procurement agencies, sections

or departments and several stages of administration, finance and technical decisions. Pharmaceutical products are not ordinary commodities of trade and require special attention. Support from the offices responsible for quality assurance is crucial. The efficiency of the procedures depends in great part on the use of a proven method in a consistent manner. The use of a standard approach will ensure consistency in all activities involved in procurement of pharmaceutical products of defined acceptable quality.

This Model focuses on the following four key activities of procurement agencies:

- prequalification of pharmaceutical products and manufacturers;
- purchase of pharmaceutical products;
- storage of pharmaceutical products; and
- distribution of pharmaceutical products.

Procurement agencies are ultimately responsible for the outcomes of all four key activities. In some cases, one or more of the activities may be contracted out. Where this occurs, a written contract which describes the responsibilities of both parties should be agreed upon between the two parties. The contract-giver remains responsible for ensuring that the contract-acceptor meets the norms and standards reflected in this Model.

Recommendations

It is recommended that procurement agencies involved in any of the key activities of procurement develop and implement their own internal quality assurance systems on the basis of the Model, including the elements described and technical details specified. It is important to ensure that the system is adapted to reflect the activities of each specific procurement agency. The system should cover all aspects of the agency's activities and should be comprehensive enough to ensure that interrelated activities which impact on the quality of pharmaceutical products are linked.

This document provides guidelines for United Nations procurement agencies, but they may also be used by other procurement agencies to establish quality assurance systems for their own activities.

These guidelines are designed for procurement of pharmaceutical products. They may also be applicable to the procurement of diagnostic kits or medical devices.

Overview

This document is divided into six modules. Module I addresses the general requirements for the quality assurance system that should be in place at all procurement agencies, irrespective of the number of key activities performed. Module II sets out recommendations that procurement agencies should implement when evaluating their product needs, assessing the products offered and the manufacturing and supply arrangements provided by the manufacturers. Module

III describes principles of purchasing pharmaceutical products. Module IV contains recommendations on how to receive and store purchased products. In Module V, good distribution practices are described and Module VI deals with monitoring and reassessment of products and contracted-out activities. This document also includes documentation examples of elements of this Model as well as relevant existing WHO guidelines.

Throughout this document, reference will be made to existing WHO norms, standards, guidelines and texts. An effort has been made to avoid duplication wherever possible. Where relevant, reference is made to related documents.

The standard text *Managing drug supply*(1) provides a complete and detailed overview of technical aspects of pharmaceuticals management, including all the key activities of procurement.

Glossary

accountability

The obligation to account for one's conduct and actions, usually to an individual or group, but ultimately to the public. Both individuals and organizations may be accountable. There is some overlap between accountability and transparency (see below).

active pharmaceutical ingredient (API)

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

affordability

The extent to which pharmaceutical products are available to the people who need them at a price they can pay.

authorized person

A person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale. In some good manufacturing practice (GMP) guides and legal texts, the term qualified person is used to describe analogous functions.

bioequivalence

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities, in terms of peak (C_{\max} and T_{\max}) and total exposure (area under the curve (AUC)), after administration in the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

bioavailability

The rate and extent at which the active pharmaceutical ingredient or active moiety is absorbed from a pharmaceutical dosage form and becomes available at the site(s) of action.

competitive tender

A procedure for procuring pharmaceutical products which puts a number of suppliers into competition. Purchasing is done on the basis of quotations submitted by the suppliers in response to a public notice.

drug

Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient. In this document, the terms *drug*, *medicine* and *pharmaceutical product* (see below) are used interchangeably.

drug legislation

The legal conditions under which pharmaceutical activities should be organized. (See also *legislation* below.)

drug regulatory authority

A national body that administers the full spectrum of drug regulatory activities, including at least all of the following functions in conformity with national drug legislation:

- marketing authorization of new products and variations of existing products;
- quality control laboratory testing;
- monitoring of adverse drug reactions;
- provision of drug information and promotion of rational drug use;
- *good manufacturing practice* (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels;
- enforcement operations;
- monitoring of drug utilization.

effectiveness

An expression of the degree to which activities have produced the effects planned.

efficiency

The relationship between the results of activities and the corresponding effort expended in terms of money, resources and time.

essential pharmaceutical products

Those pharmaceutical products that satisfy the health care needs of the majority of the population. WHO's Expert Committee on the Selection and Use of Essential Medicines updates the *WHO Model List of Essential Medicines* at two-year intervals. Each country may use this model to generate its own list of essential pharmaceutical products.

generic products

The term *generic product* has somewhat different meanings in different jurisdictions. The use of this term is therefore avoided as far as possible, and the term *multisource pharmaceutical product* (see below) is used instead. Generic products may be marketed either under the approved nonproprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different from those of the *innovator products* (see below). Where the term *generic product* is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

generic substitution

Practice of substituting a product, whether marketed under a trade name or generic name, with an equivalent product, usually a cheaper one, containing the same active ingredient(s).

good manufacturing practice (GMP)

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.

indicator

Criterion used to measure changes, directly or indirectly, and to assess the extent to which the targets or objectives of a programme or project are being attained. Indicators should meet the criteria of clarity, usefulness, measurability, *reliability*, *validity* (see below) and acceptance by key stakeholders.

innovator pharmaceutical product

Generally the pharmaceutical product which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality according to requirements at the time of the authorization. When a substance has been available for many years, it may not be possible to identify an innovator pharmaceutical product.

interchangeability

An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator (reference) product.

International Nonproprietary Name

The shortened scientific name based on the active ingredient. WHO is responsible for assigning INNs to pharmaceutical substances.

legislation

The first stage of the legislative process, in which laws are passed by the legislative body of government with regard to a subject matter, e.g. control of pharmaceuticals. Laws define the roles, rights and obligations of all parties involved in the subject matter in general terms (see also *regulations* below).

licensing system

National legal provisions on who should manufacture, import or supply pharmaceutical products, what qualifications people in the supplying agency should have, and who should dispense and sell pharmaceutical products.

manufacture (manufacturing)

All or any operations of purchase of materials and products, production, quality control, release, storage and distribution of finished products and the related controls.

marketing authorization

A legal document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf-life and storage conditions, and

packaging characteristics. It specifies the information on which authorization is based (e.g. “The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence.”). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be “registered” or to “have registration”. Market authorization may occasionally also be referred to as a “licence” or “product licence”.

medicine

See *drug*.

multisource (generic) pharmaceutical product

Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

national list of essential pharmaceutical products

The list of *essential pharmaceutical products* (see above) that has been defined, adopted and published at country level. It is normally used by all health facilities, including the main hospitals.

pharmaceutical product

See *drug*.

prequalification

The activities undertaken in defining a product or service need, seeking expressions of interest from enterprises to supply the product or service, and examining the product or service offered against the specification and the facility where the product or service is prepared against common standards of *good manufacturing practice* (GMP). The examination of the product or service and of the facility where it is manufactured is performed by trained and qualified inspectors against common standards. Once the product is approved, and the facility is approved for the delivery of the specified product or service, other procurement agencies are informed of the decision. Prequalification is required for all pharmaceutical products regardless of their composition and place of manufacture/registration, but the amount and type of information requested from the supplier for assessment by the procurement agency may differ.

procurement

The process of purchasing or otherwise acquiring any pharmaceutical product, vaccine, or nutraceuticals for human use. For the purpose of this document, *procurement* means the pre-selection of products and manufacturers through a procedure of qualification, including *prequalification* (see above) and continuous monitoring thereafter, purchase of the prequalified products from prequalified manufacturers (linked to the specific product) through defined purchasing mechanisms, storage and distribution.

procurement agency

Any organization purchasing or otherwise acquiring any pharmaceutical product, vaccine or nutraceutical for human use. In the context of these guidelines it will normally be a not-for-profit organization, a nongovernmental organization (NGO) or a United Nations organization. A *procurement agency* in the context of this document is defined as any organization purchasing pharmaceutical products, vaccines, or other health sector goods or otherwise involved in their *prequalification* (see above), purchasing, storage and distribution.

product information

In the context of this document, product information means information on pharmaceutical products submitted by manufacturers or suppliers in any of the formats specified in the procurement agency's guidelines (including product dossiers, product questionnaires or other formats) to obtain prequalification for the products.

qualification

Action of proving and documenting that any premises, systems and equipment are properly installed and/or work correctly and lead to the expected results. Qualification is often apart (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation. In the context of this document it is the work done to prove that the supply system will deliver products of the quality required and specified on a routine basis, meeting all the applicable quality requirements.

quality assurance

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

quality control

Quality control is concerned with sampling, specifications and testing, and with the procurement agency's documentation and acceptance/rejection procedures which ensure that the necessary and relevant tests are actually carried out and that starting materials, intermediates and finished products are not accepted for use, sale or supply until their quality has been judged to be satisfactory.

regulations

The second stage of the legislative process (the first stage being legislation, see above). Regulations are specifically designed to provide the legal machinery to achieve the administrative and technical goals of legislation.

reliability

An expression of the degree to which a measurement performed by different people at different times and under different circumstances produces the same results (see also *validity*).

reliable quantification of drug needs

A careful evaluation of the quantities needed of each drug, based on either adjusted past consumption or anticipated pattern of diseases and standard treatment, which can be expected to match actual needs reasonably well.

transparency

The term transparency means:

- defining policies and procedures in writing and publishing the written documentation; and
- giving reasons for decisions to the public (see also *accountability* above).

validation

Action of proving and documenting, in accordance with the principles of good manufacturing practice, that any procedure, process, or method actually and consistently leads to the expected results (see also *qualification* above).

validity

An expression of the degree to which a measurement performed actually measures the characteristic which the investigator wishes to measure (see also *reliability* above).

WHO-type certificate

A certificate of pharmaceutical product of the type defined in the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.¹

¹ World Health Organization. WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. Geneva, World Health Organization, 2000. WHO/EDM/QSM/2000.2. (<http://www.who.int/medicines/organization/qsm/activities/drugregul/certification/certifschemes.html>).

Module I

General requirements for procurement agencies

Introduction

Procurement agencies often have to purchase and supply pharmaceutical products using scarce resources. In many cases, product quality is compromised when products are obtained from unqualified sources. Procurement agencies will deal with various types of suppliers and customers, including drug regulatory authorities, manufacturers, quality control laboratories, contract manufacturers, contract laboratories, traders, brokers, distributors and pharmacies. A quality assurance system will assist in ensuring that transactions with these partners ultimately result in procuring pharmaceutical products of the best possible quality.

This module addresses the general requirements for such a system, including physical resources such as premises, equipment and personnel, as well as the documented policies, standards and procedures required to ensure consistency in all the key activities of procurement. The general requirements described in this module are therefore applicable to all the activities covered in subsequent modules.

I.1 Physical resources

I.1.1 *Premises*

Offices

The procurement agency should have sufficient office space to accommodate the personnel required and the activities to be performed.

Storage

The procurement agency should have sufficient space for storage and retention of commodities, including product documentation, product samples, stock, reports, files and other records relating to all key activities of procurement.

Samples and products should be stored under suitable conditions which are specified, e.g. with regard to temperature, humidity or protection from light. Details of storage requirements are given in Module IV.

There should be sufficient space for storage of equipment, stationery and materials for proper distribution. Details of distribution requirements are given in Module V.

1.1.2 **Equipment**

Computers

The use of computers can facilitate, but not replace, efficient procedures in pharmaceutical procurement. When implemented appropriately, computerization will speed up complex tasks, increase accuracy and automate repetitive tasks. Staff must be trained adequately in the use of computerized systems.

Many aspects of procurement are suitable for computerization, including planning of requirements, budget management, financial analysis, preparation of documentation and reports and inventory control. Hard copies (printouts) should be produced as required to provide documented evidence of the activities.

Where computer systems are not used, manual systems should provide documented evidence of the activities performed.

Software

The software selected should be suitable for the intended use. The programmes used should be able to provide the required quality and management information reliably and accurately. They should be user-friendly and staff should be trained adequately in their use. Where possible, different programmes used should be compatible so that data can be transferred between them without having to be retyped.

Where information is exchanged between the procurement agency and the manufacturer(s) by electronic means, appropriate programmes should be in place.

Suitable security systems should be in place to prevent unauthorized access or changes to computer records and reports. Back-up systems must be in place to prevent loss of data. A good-quality virus protection programme and firewall must be installed, configured, used and updated regularly to prevent unauthorized access and loss of data.

Technical support should be available to ensure that software and security systems are kept functional and up to date.

Hardware

The hardware selected which should be able to handle the required software efficiently. The system should have sufficient capacity and memory for the intended use, as well as adequate input and output devices, including good quality printers. Access to the Internet and possibly to an internal network (LAN) should be provided to facilitate exchange of information.

A maintenance and upgrading plan must be in place to ensure that the system remains functional.

Telecommunications

There should be access to telephone and facsimile facilities to ensure instant communication. If at all possible, electronic mailing (e-mail) systems should be available.

Furniture

Suitable office furniture should be provided, including desks, chairs, shelves, cupboards, filing cabinets and other items as required.

Office equipment

Office equipment including copying machines, staplers and punches should be provided.

1.1.3 Materials and consumables**Stationery and consumables**

The procurement agency should provide stationery to enable staff to perform the relevant tasks, including paper, letterheads, business cards and pre-printed forms as required. Computer consumables to be provided include removable storage devices (floppy disks, CDs and/or flash memory sticks), printer cartridges, printing paper, as well as any replacement parts not covered by a maintenance contract.

Vehicles and transport

Official transport or reimbursement of transport costs incurred should be provided for trips to meetings, visits, inspections and performance of other official duties.

In cases where the procurement agency is responsible for local transportation and distribution of products, appropriate transport should be provided to ensure that the quality of the products is maintained.

1.1.4 Financial systems

The procurement agency should be able to effect national and international financial transactions as required. Funds must be available to ensure continued operations, whether or not cost recovery mechanisms for key activities, e.g. prequalification, are in place.

Adequate banking facilities must be available. Signatories of bank accounts should be appointed to ensure control on one hand, and continuity of operations during the absence of key personnel on the other hand.

An accounting system should be in place. Regular financial audits should be performed.

If the procurement agency is part of a larger organization, it should have sufficient autonomy and/or sufficiently good communication with the mother organization's

financial department to enable it to conduct all its financial transactions without delay.

I.1.5 Human resources

Personnel

There should be a sufficient number of appropriately trained, educated and experienced personnel to perform the key activities. The number of members of staff required in the department responsible for the key activities will depend on the volume and value of products sourced and to be supplied. Sufficient support staff for secretarial, organizational and accounting duties as well as legal support should also be available.

Key personnel should include those responsible for prequalification, purchasing, storage and distribution. The person responsible for prequalification could also be responsible for quality assurance. National legislation should be complied with, e.g. requirements for a responsible person for purchasing, storage and distribution of pharmaceutical products.

The person responsible for prequalification and the person responsible for purchasing should be independent of one another. One should not report to the other.

The responsibilities of the staff in charge of the different key activities are described in Modules II to V.

Qualifications and experience

Personnel responsible for prequalification, purchasing, storage and distribution should have sufficient qualifications, knowledge and experience of their respective fields (see Modules II to V).

Code of conduct

All staff members should comply with a code of conduct which should guide all their professional activities. More detail on codes of conduct is given in section I.2.4. An example of a code of conduct is shown in Appendix 1.

Confidentiality

It is essential that all information obtained by any person working for the procurement agency is treated as confidential. Most of the information obtained from companies and manufacturers is product-specific, may be patented and will be commercially sensitive. The evaluators and inspectors must treat all information submitted and observed during the assessment of product dossiers and inspections at manufacturing sites, and otherwise in connection with the discharge of their responsibilities in regard of the above-mentioned project, as strictly confidential and proprietary to the party collaborating with the procurement agency.

Confidentiality agreements should be signed by assessors and inspectors. An example

of such an agreement is attached in Appendix 2. Additional information may be found in Appendix 3 (example of a guideline on conflict of interest).

Conflict of interest

Before undertaking any work, assessors and inspectors (including contracted personnel) should sign a declaration of interest. If, based on their declaration of interest, it is deemed appropriate for them to undertake the work specified, they agree to carry out their functions exclusively for the agency. They should confirm that the information disclosed by them in the declaration of interest is correct, that no situation of real, potential or apparent conflict of interest is known to them and that they have no financial or other interest in, and/or relationship with a party which:

- may have vested commercial interest in obtaining access to any confidential information disclosed to them in the course of the evaluation activities described in the declaration; and/or
- may have a vested interest in the outcome of the evaluation activities including, but not limited to, parties such as the manufacturers whose products are subject to evaluation or manufacturers of competing products.

Personnel should undertake to advise the procurement agency promptly of any change in the above circumstances, for instance if an issue arises leading to a conflict of interest during the course of their work for the procurement agency.

Job descriptions

There should be written job descriptions, with definitions of responsibilities, for all personnel.

Organizational structure

The procurement agency should have an organization chart indicating the positions, names of responsible persons and reporting lines.

The organization chart should reflect the responsibilities and reporting lines in accordance with the job descriptions.

1.2 Documentation of policies and standards

Documentation is a critical part of a quality assurance system. The procurement agency should have a comprehensive documentation infrastructure, which should include policies, guidelines, norms, standards, manuals, procedures, records and related documents.

All activities of each section or department should be performed and documented in a standardized manner, following approved written procedures.

The main elements of the documentation system of this Model are described below.

1.2.1 **Quality manual**

The procurement agency should have a quality manual. The purpose of such a manual is to document the quality policy as defined by management in relation to the various activities undertaken by the procurement agency. There should be policy statements and a quality policy in terms of the agency's activities and objectives, as well as documents describing the policy of each section or department with regard to all activities in prequalification and subsequent purchasing, storage and distribution.

Once this quality policy is defined, it should be implemented, maintained, reviewed and amended as necessary at regular intervals by the procurement agency.

1.2.2 **Standard operating procedures**

The procurement agency should have written, clear and detailed standard operating procedures (SOPs) for all the activities to be performed in the procurement agency. The content of each SOP, particularly the step-by-step descriptions of activities and approved recording or reporting formats attached as addenda (see below), should reflect the operations of the particular procurement agency.

SOPs should be drafted by the person responsible for the procedure. An SOP for writing an SOP should be followed to ensure consistency of design, format and layout. An SOP on how to write an SOP is attached as Appendix 4.

Style and layout

SOPs should be written in the procurement agency's approved format, and be formally approved (signed and dated) by the authorized person(s).

SOPs should be written in clear, unambiguous language.

The name and/or logo of the procurement agency should be included on the front page of each SOP.

Elements of standard operating procedures

The SOP should contain at least the following elements.

Title and number

Each SOP should have a title. The title should give a clear indication of the activity which it describes. A numbering system is useful to identify to which activity or department the SOP refers.

Objective

This section should describe what is to be accomplished and/or achieved with the SOP.

Scope

This section should describe to what level or depth, or how widely, the SOP is applicable.

Policy

This section should reflect the procurement agency's policy regarding this particular activity.

Responsibility

This section should list the person(s) responsible for performing the activities listed in the procedure. It may be useful to refer to the position rather than the name of the person.

Action

This section should describe the sequence of action steps to be followed, from the beginning to the end of the process, to perform the activity.

The action steps should be written in the imperative and should be numbered. It is advisable to indicate who is responsible for each step. This could be done by putting the position (job title) of the responsible person in brackets next to each step, or by indicating the numbers of the relevant steps next to the positions listed under the heading "Responsibility".

Where a step leads to another procedure to be followed, the applicable SOP should be referred to in that particular step.

Distribution and retrieval

Documentation should be distributed with care. No superseded or obsolete SOPs should be available at user points. The sections and/or responsible persons (positions) to whom the SOP was distributed should be listed. Each time the SOP is reviewed and amended, superseded versions of the SOPs should be removed from all the user points listed and replaced with the updated version; the retrieval should be documented.

Revisions

In a section which could be headed "History", the date of each change to the SOP, the person responsible for the review, the change itself and the reason for the change should be recorded. This section will provide the procurement agency with the history of the amendments to the SOP.

Addenda

Any records to be completed or maintained as part of the activity should have a standardized format. It is useful to define and approve these formats in advance. The approved standard format should be part of the SOP and can be attached as an addendum to the SOP.

Activities to be covered by standard operating procedures

The following list gives examples of activities which could be covered by SOPs:

- how to write a standard operating procedure (see Appendix 4);
- drafting a contract or agreement;
- amendments to contract or agreement;
- identifying and reporting counterfeit products;
- reporting of deviations;
- appointing evaluators of product information;

- appointing contract inspectors;
- maintaining a master documentation list;
- receiving and screening of an offer received;
- evaluating offers received;
- ordering product(s) from supplier or manufacturer;
- publishing specifications of products for procurement;
- sending out, receiving and evaluating supplier questionnaires;
- handling recalls;
- policy for regular re-inspection;
- routine follow-up of inspections;
- inspection fault correction; and
- standard formats for inspection reporting.

1.2.3 ***Change control policy***

The procurement agency should have a policy for change control. This policy should be designed to manage changes in the agency's own procedures and documentation, as well as changes in data and information on the pharmaceuticals to be prequalified.

A procedure for controlling changes that affect APIs, formulation, manufacturing processes, analytical testing methods or packaging of prequalified products is essential. The procedure should ensure that these changes are reported to the procurement agency before new batches are manufactured or before they are delivered and released for distribution. Details of managing changes in product information are given in Module VI.

1.2.4 ***Code of conduct***

The procurement agency should design, authorize and implement a written code of conduct.

The code of conduct should describe the policy of the procurement agency regarding the conduct of staff in respect to their activities. It should be followed by all personnel.

The code of conduct should give guidance to staff members on appropriate conduct in various situations. The following topics could be covered in the code:

- introduction and objectives;
- key responsibilities;
- personal responsibilities;
- safety;
- professional competence;
- qualifications and experience;
- conduct;
- integrity and attitude;
- attire, health and hygiene;
- management relationship;
- SOPs;

- travel and accommodation;
- confidentiality and conflict of interest;
- documentation and records;
- contracts and terms of reference (TOR);
- product files, evaluation and inspection;
- samples;
- evaluation and inspection reports; and
- provision of information and advice.

1.2.5 ***Guidelines on conflict of interest***

The procurement agency should have a policy on conflict of interest which all personnel should observe. An example of a guideline on conflict of interest is shown in Appendix 3.

The document should address at least the following points:

- introduction and objectives;
- definitions and principles;
- responsibilities;
- confidentiality; and
- impartiality.

1.2.6 ***List of prequalified products and manufacturers***

The procurement agency should have a procedure for drafting and maintaining a list of prequalified products and manufacturers, based on the outcome of the evaluation of product data and information and manufacturing site inspections. The list should be product- and manufacturing site-specific, i.e. sites are prequalified for one or more specified products, and products are prequalified as manufactured at specified sites.

The key person responsible for prequalification should be responsible for addition to and/or deletions from the list.

Once the evaluation of a product dossier is complete, and the inspection has been performed to assess compliance with good manufacturing practices, good storage practices and good distribution practices as appropriate, the procurement agency should prepare a list reflecting the status of the prequalified products and manufacturers.

The list should contain at least the following information:

- name of the procurement agency;
- authorization signatures;
- reference number and version of the list;
- date of preparation of the list;
- name and physical address of manufacturer, including the approved site(s) of manufacture linked to each product;
- contact details, including postal address, telephone, fax number and e-mail address of the manufacturer and supplier;

- product details, including the brand name, INN, dosage form, strength per dose and pack size;
- date of original prequalification;
- date of expiry of the prequalification; and
- date until which the list is valid.

1.2.7 **Maintenance of records**

Records of all operations should be maintained and kept in a suitably organized manner.

Sufficient areas for the storage of records, including product information, manufacturers' information and inspection reports, should be available.

Access to these areas should be restricted to authorized personnel only, as confidential information may be filed (including records of manufacture, testing and/or storage).

Records should be maintained for a defined period of time, in accordance with national legislation. Generally they should be retained for at least one year beyond the expiry date of the finished product.

Module II. Further guidance on record-keeping in quality assurance systems is provided in the WHO publication *Quality assurance of pharmaceuticals* (2, 3).

Module II

Prequalification

Introduction

Prequalification is one of the key elements in ensuring purchase and supply of pharmaceutical products of acceptable quality. The prequalification process can be subdivided into two major parts, i.e. product-related assessment and manufacturer-related assessment.

- *Product-related assessment* should ensure that the correct product is specified by the procurement agency. The procurement agency should then assess whether the manufacturer is offering a product that meets the predetermined norms and standards in terms of safety, quality and efficacy.
- *Manufacturer-related assessment* should ensure that the manufacturer is able to manufacture the product as specified in the product information package and in accordance with good manufacturing practices (GMP) as recommended by WHO. The manufacturer must be capable of routinely carrying out the activities to the specified standards to ensure batch-to-batch consistency of the product.

Assessment of contracted-out services, e.g. by storage and distribution agents, contract research organizations (CROs) and quality control laboratories for compliance with GMP, good clinical practices (GCP) and good laboratory practices (GLP), are further elements that may supplement the prequalification process.

The procurement agency is responsible for ensuring that all steps in the prequalification process are carried out in accordance with this Model. This should ensure that the manufacturers will be providing products as specified that meet all predetermined norms and standards. It will assist procurement agencies in maximizing the use of resources and will avoid duplication of prequalification by different procurement agencies. It should also minimize the risk of procurement agencies purchasing and supplying substandard products.

This module sets out recommendations which procurement agencies should implement when evaluating their product needs and when assessing the products and the manufacturing and supply arrangements offered by the manufacturers.

II.1 Principles for prequalification

Prequalification procedures should be based on the following principles:

- reliance on the information supplied by the national drug regulatory authority;
- evaluation of product data and information submitted by manufacturers, including product formulation, manufacture and test data and results;
- a general understanding of the production and quality control activities of the manufacturers and suppliers and of their commitment to the principles of GMP;

- assessment of consistency in production and quality control through compliance with GMP as described in the WHO publication *Quality assurance of pharmaceuticals*, Volumes 1 and 2 (2, 3) and supplementary WHO GMP guidelines;
- availability of appropriate quality systems and SOPs;
- random sampling and testing of pharmaceutical products supplied;
- adequate purchasing mechanisms (see Module III);
- good storage practices (see Module IV);
- good distribution practices (see Module V);
- monitoring of complaints from procurement agencies and countries;
- adequate handling of complaints and recalls; and
- continuous monitoring and requalification.

The procurement agency should have a document describing the policy and procedures for prequalification, including the assessment of product information and of manufacturers for compliance with standards.

II.1.1 **WHO Model List of Essential Medicines**

Procurement agencies may find that many of the products they require are on WHO's Model List of Essential Medicines, which contains medicines of proven safety and efficacy and is updated periodically (4). Procurement agencies should focus on procurement of medicines reflected in the Model List. They will find this list a useful reference for establishing specifications for the medicines needed for their purposes.

II.2 **Standards for prequalification**

The prequalification procedure should be based on the Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations Agencies (5). In principle, products should meet at least the recommendations made by WHO in *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products – a manual for drug regulatory authorities* (6). Manufacturing sites should comply with at least WHO GMP (3).

II.3 **Key persons and responsibilities**

II.3.1 **Staff responsible for prequalification**

The person responsible for prequalification should be independent from the person responsible for purchasing.

The key responsibilities of the person responsible for prequalification activities should include the following:

- establishing specifications for products;
- publication of invitations for expressions of interest (EOI);
- preparation of a questionnaire for collecting product data and information and/or guidelines for the — compilation of product information;

- assessment of product data and information for compliance with norms and standards;
- assessment of manufacturing sites, through inspection, for compliance with WHO GMP; and
- preparation of the list of prequalified products and manufacturers.

II.3.2 ***Staff responsible for evaluation of product information***

The person responsible for evaluation of product information should be independent from the person evaluating the manufacturing site. Neither should report to the other in terms of decision-making.

The key responsibilities of the person responsible for evaluating product information should include:

- preparing and implementing SOPs and guidelines for evaluation of product information;
- receipt of product information;
- screening of product information;
- evaluation of product information;
- informing manufacturers of the outcome of the evaluation of the product information; and
- communicating with the person responsible for inspections of manufacturing sites.

The person responsible for the evaluation of product information may be a member of the existing staff or appointed for this task.

The people assigned to evaluate product information should have relevant qualifications and experience, including a background in pharmaceuticals, pharmaceutical chemistry and pharmacology. Ideally they should be from a regulatory background, or have regulatory experience.

II.3.3 ***Staff responsible for inspection of manufacturing sites***

The key responsibilities of the person responsible for inspection of manufacturing sites should include the following:

- preparation and implementation of guidelines and SOPs;
- coordination of inspections to be performed;
- recruiting or appointing inspectors with appropriate qualifications and experience when necessary;
- training of inspectors;
- organization of inspections;
- finalizing inspection reports; and
- informing manufacturers of the outcome of the inspection.

As a minimum, the personnel responsible for inspecting manufacturing sites should have relevant qualifications and experience in pharmaceutical manufacturing, quality assurance, GMP, performing inspections and audits, chemistry and quality control. Ideally they should have an inspection background from working with a regulatory authority.

Although decision-making should be independent, there should be communication between the person responsible for evaluation of product information and the person responsible for inspection of manufacturing sites, as some information on the product may have to be verified during the site inspection.

II.4 Key steps in prequalification

The key steps in prequalification are summarized in Fig. 1. Detailed descriptions of the different steps are given below. The preparatory steps of drafting a documentation system, including confidentiality agreements, declaration of conflict of interest, SOPs and guidelines, are described in Module I.

II.4.1 **Step 1: solicit and receive expressions of interest**

Draft product specifications for prequalification

Specifications for the product(s) to be prequalified should be drafted with input from the person responsible for purchasing, so that the product meets the requirements for the intended purpose.

The specifications should be detailed, clear and unambiguous to avoid unnecessary submission and processing of documentation not relevant to the product to be sourced.

The specification should state at least:

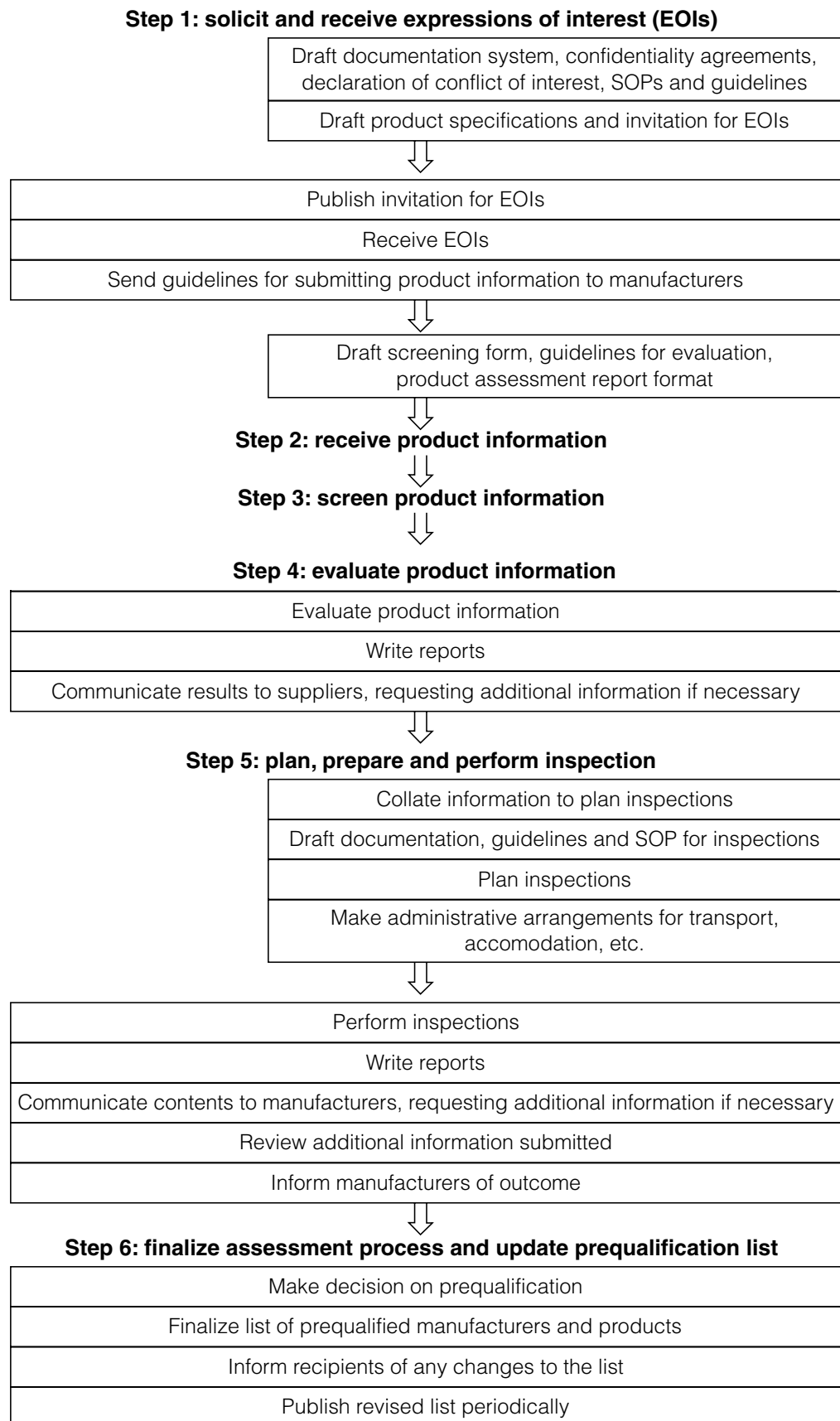
- the name of the active pharmaceutical ingredient(s);
- pharmacopoeia reference (if any), e.g. European Pharmacopoeia, Japanese Pharmacopoeia, United States Pharmacopoeia and International Pharmacopoeia;
- strength per dose and dosage form;
- dosage form (route of administration);
- pack size;
- packing material; and
- labelling requirements.

The specification could be published as part of the invitation for EOIs.

Draft and publish invitation for expressions of interest

Once the specification is finalized, an invitation for EOIs should be published widely to reach any manufacturers that may be interested in supplying the product(s).

Figure 1

Key steps in prequalification

The process of inviting all interested manufacturers to submit their EOI for the pharmaceutical products listed should be open and transparent. Invitations for EOIs may be published for groups of products, and may be repeated as necessary.

The invitation for EOIs should be detailed and should state at least:

- the purpose of the invitation for EOIs;
- the objective of the invitation for EOIs;
- the list of products, including specifications for each product;
- information on quantities required (if available);
- details of the information to be submitted;
- guidelines for submission, including information on details to be submitted as part of the EOI, on the focal point for the submission and on the format for the submission;
- contact details (name, address, telephone number, fax, e-mail and postal address) for submission of the EOI; and
- the closing date for receipt of the EOI by the procurement agency.

An example of an invitation for EOIs is shown in Appendix 5.

Manufacturers should submit their EOI with the requested information about the product(s) and manufacturer(s), before the date specified by the procurement agency.

Receive expressions of interest

The procurement agency should ensure that the relevant infrastructure exists for the receipt and processing of the EOIs through the subsequent prequalification steps.

The procurement agency should have a clear policy regarding the acceptance of EOIs after the specified closing date. Processing of late submissions should not normally be allowed. Only in exceptional instances should late EOIs be considered, e.g. when a manufacturer is the only one to express an interest in supplying a specific product.

It would be appropriate to express concern at the late arrival of the EOI, and manufacturers should give reasons for late submission.

A record of all the EOIs received from each manufacturer should be maintained.

Send guidelines for submitting product information to manufacturers

Manufacturers who have submitted an EOI before the closing date specified in the invitation should be given guidelines for the compilation and submission of information on products and manufacturers. The guidelines should be publicly available and accessible. In cases where this is not done, reasons for the decision should be given and documented.

The guidelines should be written in clear, unambiguous language. Guidelines should contain information including at least:

- the content and format of submission, including the type and format of

information required (e.g. the procedure for submission of information for a product registered in a country recognized as having an effective drug regulatory agency, and instructions for cross-referencing an existing dossier with the prescribed submission format); and

- the process of submission, including the address to which the documentation should be sent and a statement of any fees payable for cost recovery.

Content and format of submission

For each product to be prequalified, interested manufacturers should be asked to submit product information, together with a sample of sufficient quantity to allow analyses of the product against its finished product specification as stated in the product information, a covering letter (as recommended on the EOI) and a checklist for the product information.

Depending on the active ingredients, country of manufacture and registration of products to be prequalified, different formats for submission will be required.

Detailed information should be submitted for products for which bioavailability may be altered by chirality, isomerism, controlled release formulation, polymorphism or other properties which may affect the therapeutic outcome.

In this document, the term “product information” refers to any of the following four formats, in which submissions should be made:

1. A product dossier, which should be submitted for multisource (generic) products, for innovator products which have been on the market for less than five years, and for products containing substances that have specific properties that may have explicit impact on the safety, efficacy or quality of the product. The “*Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant*” (7) may also provide a helpful example of guidelines for this type of submission.
2. A standard product dossier as prepared for a national drug regulatory authority can be submitted, provided it contains the appropriate information as required in these guidelines. In such cases, the supplier should provide a covering letter which indicates where the required information can be found in the standard product dossier.
3. For products manufactured and registered in countries where regulatory requirements are in line with international regulations for assessment of safety, efficacy and quality, the following information should be submitted:
 - a WHO-type certificate of a pharmaceutical product (CPP) (8) issued by one of the regulatory authorities of an International Conference on Harmonisation (ICH) region (European Union, Japan or the USA), together with a summary of product characteristics (SmPC);
 - an assessment report issued by the regulatory authority;
 - a WHO-type batch certificate from the manufacturer.

If the packaging of the product is different from that approved by a regulatory authority of an ICH region, stability testing data should be submitted. If the

formulation, strength or other specifications are different from the product for which the WHO-type product certificate (CPP) was issued, arguments and/or data to support the applicability of the certificate despite the differences should be submitted.

4. A completed questionnaire with limited information on the product should be submitted for products containing only substances that do not have specific properties that may have explicit impact on the safety, efficacy or quality of the product. An example of a pharmaceutical product questionnaire is shown in Appendix 6.

Information about the site(s) where each product is manufactured will also be required at a later stage. For guidelines on submission of information on manufacturing sites, see “Planning and preparation of inspections”.

The same process as outlined above should be followed for suppliers who perform only part of the supply process. This is particularly relevant where a product from a prequalified manufacturer is to be supplied through a new distribution channel. For example, a procurement agency might wish to ship an already prequalified product to a new country using new traders, brokers or distributors. The organizations involved in the new distribution channel will need to be appropriately prequalified. Depending upon the nature of the supply arrangement, the requirements for product information and the GMP inspection process may be modified.

Process of submission

Suppliers should be allowed at least 60 days for the compilation and submission of product information.

Suppliers should be requested to submit a covering letter, containing a clear statement by the responsible person that the information submitted is true and correct.

The procurement agency should reserve the right to terminate the prequalification procedure of a product and manufacturer if the manufacturer fails to provide the required information in a specified time period, or if the information supplied is inadequate to complete the prequalification effectively.

11.4.2 Step 2: receive product information

The procurement agency should have the necessary infrastructure to receive and process the product information submitted by manufacturers. It will require personnel for processing the documentation; written procedures for receiving, identification, marking files, containers and samples, and sufficient space for unpacking and storage.

Containers with product information should be received at the specified address before a specified date as determined by the procurement agency.

Containers should be opened in the presence of at least two people. A record should be kept of the names of the people who opened the containers and the contents of the containers.

Each product should be allocated a unique reference number to ensure traceability of the product information.

II.4.3 **Step 3: screen product information**

Each product information package submitted by the manufacturer should be screened for completeness. The screening should be done in accordance with a written procedure. If the product information submitted fails to meet the requirements, it should be excluded from the evaluation procedure and inspection process.

A screening form should be used to ensure consistency of screening. There should be a written record of the screening of each product information package. Information to be recorded should include:

- date of receipt;
- name of the interested manufacturer(s);
- address of the manufacturer;
- name of the product;
- country of manufacture;
- product number; and
- outcome of the screening.

An example of an SOP for screening and assessing product information, including a sample screening form, is shown in Appendix 7. Incomplete information should not be kept for evaluation purposes. The manufacturer should be informed that an incomplete information package was received, and be requested to supply the missing information within a specified period. If this request is not complied with, the application should be rejected on grounds of incompleteness.

Product information packages which meet the requirements of the screening procedure should be retained for full evaluation.

A summary should be made of each product information package received, stating any reference number allocated to the product by the procurement agency, the INN, strength, dosage form and pack size of the product, the name of the supplier, the name and address of the manufacturing site(s), whether a sample has been submitted, and if so, the sample size.

II.4.4 **Step 4: evaluate product information**

Evaluators

Evaluators with suitable qualifications and experience in the evaluation of product data and information should be available to conduct the assessment. Suitably qualified external evaluators may be appointed. Appointment of external evaluators should be subject to compliance with the policy of the procurement agency, regarding aspects such as confidentiality, conflicts of interest and financial resources. Examination of potential conflicts of interest and confidentiality must go beyond the potential evaluator signing a declaration. Checks on references should also be made.

A formal agreement for the performance of work and terms of reference for contracted evaluators should be in place before commencement of work.

A summary list of names, addresses, dates of appointment, qualifications and experience of evaluators should be maintained. Copies of signed agreements should be kept in a central file.

Evaluation

Time frames should be set for evaluation of product information. Product information should be evaluated within 21 days after the closing date for submission.

A written procedure for evaluation should be followed. An example of an SOP for screening and assessing product information is attached as Appendix 7.

The person responsible for evaluation should monitor the process to ensure that each product information package is evaluated in compliance with these requirements. Information on the product's patent status should be considered to avoid infringement of intellectual property rights (see also Section III.7).

Contract research organizations should be inspected as part of the assessment process to ensure that bioequivalence studies have been done in accordance with GCP and GLP, and that tabulated data submitted to prove bioequivalence accurately reflect the generated raw data.

Evaluation reports

Each evaluator should prepare a formal evaluation report for each product, including a recommendation for acceptance or rejection. The evaluation report should be communicated to the manufacturer within 14 days of the evaluation.

A response should be invited from the manufacturer in cases where data and information are found to be incomplete or do not meet the guidelines. A period of at least 60 days should be allowed for submission of additional data and information.

This additional information should be assessed and the final outcome of the evaluation should be communicated to the manufacturer.

The evaluation report should be filed with the product evaluation documentation for reference purposes and follow-up where relevant.

Analysis of samples

Samples submitted together with product information packages should be analysed in accordance with the finished product specification. Certificates of analysis of final products released by the manufacturer should be made available to the procurement agency on request.

The procurement agency should have access to a quality control laboratory to perform the analyses. The *WHO Guide for a quality systems manual in a control laboratory* (9) seeks to establish a practical basis for the quality systems manual of a

control laboratory which each country can adopt and adapt to prepare its own more detailed manual to meet the required level of specificity and complexity.

A laboratory may be contracted to perform the analyses. In that case, the procurement agency should ensure that the laboratory complies with GMP and good practices for control laboratories (10). The use of an accredited laboratory is therefore recommended. The procurement agency should verify the accreditation. There should be a written contract or agreement between the procurement agency and the contract laboratory. The wording of the contract should be clear and it should specify the responsibilities of the contract-giver and the contract-acceptor.

The procurement agency is responsible for ensuring access to raw data.

The procurement agency should have a procedure for investigating, handling and reporting out-of-specification results when these are obtained from laboratories. If a sample fails to meet the specifications, the procurement agency should investigate the problem and communicate the outcome to the manufacturer.

II.4.5 ***Step 5: plan, prepare and perform inspections***

Each batch of every product procured by a procurement agency should be manufactured in compliance with GMP to ensure batch-to-batch consistency. The actual site of manufacture of the product should be known and specified. In some cases, a contract manufacturer may manufacture the product on behalf of the supplier or agent. Each manufacturing site specified in the product information should be inspected to assess compliance with WHO GMP.

Manufacturers of the active pharmaceutical ingredients (APIs) used should be inspected as part of the assessment procedure to ensure that the APIs were manufactured in accordance with GMP.

Existing certificates

ISO certification is not an assurance of compliance with GMP and is not a replacement or substitute for verification of compliance with GMP.

Similarly, a CPP is not a guarantee of compliance with GMP. Participation in the WHO Certification scheme (8) is a voluntary process, and there is no formal assessment or evaluation of drug regulatory authorities entering the scheme. In some cases, reliance on the CPP alone is therefore not recommended. The certification scheme is an administrative tool and is reliable only where the relevant national drug regulatory authority has an established system which is known to comply with acceptable standards for evaluation and registration/licensing of products and manufacturers, including products for export markets. Information in addition to the CPP, e.g. a copy of the inspection report and corrective action plan from the manufacturer, may be requested. These documents, in addition to other documentation, may be considered useful in the prequalification process and in follow-up assessment or evaluation at a later stage.

The procurement agency should still verify compliance with WHO GMP as part of the prequalification procedure, and an inspection of the manufacturing site must be considered in every case.

Inspectors

Inspections should be performed by a suitably qualified, experienced inspector or team of inspectors with relevant qualifications, training and experience in performing inspections in foreign countries. Inspectors should have sound knowledge of quality assurance and GMP in pharmaceutical product production and quality control. A sufficient number of inspectors should be appointed to carry out inspections within predetermined timeframes.

Where possible, a representative from the procurement agency (the person responsible for prequalification with a knowledge of GMP) should be part of the inspection team.

In exceptional cases, consultants from the private sector may be appointed to perform inspections, provided that there is no conflict of interests and that all confidentiality undertakings are agreed upon and maintained. For these reasons, persons working in a manufacturing company may not be considered suitable. Interested external inspectors should submit their letters of interest and curriculum vitae to the procurement agency. The agency should review the documentation before deciding to appoint any inspectors. A formal agreement for the performance of work and terms of reference should be in place before commencement of work by contracted inspectors.

A summary list of names, addresses, dates of appointment, qualifications and experience of inspectors should be maintained.

Planning and preparation of inspections

In preparation for the inspection, the procurement agency should ensure that the manufacturers who have submitted EOIs to supply products are listed in a recording system for inspection planning purposes.

To facilitate planning and to save costs, manufacturers should be grouped together by country. In some countries, one manufacturer may have different manufacturing sites in addition to the submitted address of the headquarters.

Manufacturers should be informed of tentative inspection dates, and should be requested to submit information about each manufacturing site to be inspected. This information should normally be provided in a site master file (SMF). An example of a technical questionnaire for pharmaceutical manufacturers is attached as Appendix 8. This information will be used during the preparation for the inspection and during the inspection itself to verify information supplied by the manufacturer to the procurement agency.

An example of a standard operating procedure for planning an inspection is shown in Appendix 9.

As the manufacturer will be inspected as part of the prequalification process for specific products to the procurement agency, inspectors should prepare for inspections by studying the product information submitted by the manufacturer. Appendix 10 contains an example of an SOP for preparing for an inspection.

A site visit before deciding whether a GMP inspection should be performed may in some cases be appropriate. This visit is optional and does not lead to the requirement for the performance of the inspection being waived.

Performing inspections

Inspections should be performed in accordance with a written procedure. The inspection should cover all aspects of GMP. An example of an SOP for performing an inspection is shown in Appendix 11.

Information submitted in relation to the supply of the API, formulation of the product, manufacturing method and stability data should also be verified during the inspection.

The inspection should cover the evaluation and assessment of the documentation, premises, equipment, utilities and materials. It should also cover verification of data and documentation such as results, batch records, compliance with SOP and information submitted on the manufacturing method, equipment and aspects including (but not limited to) validation of the manufacturing process, validation of utilities and support systems, and validation of equipment.

If checklists are used, these should be drawn up and agreed upon for use by collaborating procurement agencies implementing this Model. An example of a GMP checklist is shown in Appendix 12.

Waiving of inspections

The need for an inspection may be waived where an inspection report is available from inspectors representing national drug regulatory authorities for the manufacturing site under consideration, covering activities for the product(s) being prequalified, provided that the report satisfies the agency that:

- all aspects of GMP for the relative product(s) have been covered;
- the inspection report is not older than 24 months;
- there is a statement from the manufacturer that no major changes have been made to premises, equipment and key personnel since the inspection by the medicines regulatory authority;
- the reports of the national drug regulatory authority demonstrate that the manufacturer has a history of compliance with GMP; and
- the inspection report has a favourable outcome.

Inspection report

Each inspector or inspection team (where inspection teams are performing inspections) should prepare a formal inspection report for each manufacturing site inspected.

The inspector or inspection team should make a recommendation on the status of the manufacturer in relation to compliance with GMP. According to the findings, the recommendation following the inspection may for example be one of the following:

- The manufacturer is considered to be operating at a reasonable level of compliance with WHO GMP and a follow-up inspection is recommended to verify implementation and acceptability of corrective actions prior to participation in any tender.
- The manufacturer is considered to be operating at an acceptable level of compliance with WHO GMP.
- The manufacturer is considered not to be operating at an acceptable level of compliance with WHO GMP.

The inspector or inspection team(s) will finalize a report according to the recommended format. The WHO *Guidance on Good Manufacturing Practices (GMP): inspection report (11)* (see Appendix 13) provides information on how to write an inspection report.

A copy of the inspection report should be filed in a central manufacturer's file that is unique to that manufacturer.

The inspection report should be communicated to the manufacturer. Where non-compliance was observed, corrective actions and time lines for completing them should be suggested. A response with supportive documentation should be invited from the manufacturer.

If any additional information is required, or if corrective action has to be taken, a final recommendation as to the acceptability of the product and manufacturer should be made only after such information has been evaluated, or the corrective action has been verified.

In the event of any dispute, a standard procedure should be followed for discussing and resolving the issue.

The ownership of the report should be with the procurement agency, as it is responsible for the prequalification.

11.4.6 Step 6: finalize assessment process and update prequalification list

Decision-making process for acceptance or rejection of a manufacturer

The procurement agency should follow a written procedure to collate the outcomes of the evaluation of product information, laboratory results for samples analysed and inspection reports.

The SOP should also identify the people responsible for taking the decision to accept or reject a product and/or manufacturer, including the grounds for the decision. It may be helpful to refer to the person by position, rather than by name.

The procurement agency should inform the manufacturer in writing of the outcome of the prequalification of each product manufactured at each specified site.

Recording of outcomes

The person responsible for prequalification should record the outcome of the prequalification process in a list of prequalified products and manufacturers. The list should include only those products evaluated as indicated by the manufacturer and listed in the EOI. It should be product- and manufacturing site-specific.

The list should be published in the public domain and should include at least the following information.

General information

- Norms and standards used;
- reference to the general procedure for prequalification;
- a statement to indicate that the list is not comprehensive for any disease category, but includes only those products submitted by possible suppliers and prequalified by the procurement agency;
- a statement to indicate that the purchaser of products from the list should ensure that only prequalified products (i.e. the same formula, manufacturing methods, manufacturing site, etc. as in the product information submitted) will be supplied by the supplier through contractual agreement between the buyer and the supplier;
- a statement that being on the list does not guarantee contracts or sales to the suppliers;
- a statement that the list should not be used by suppliers as a marketing tool to generate business;
- date of publication; and
- period of validity.

Product information

- Products and their manufacturing sites where products and manufacturers meet the standards set for the prequalification, including the following specifications:
 - INN of active ingredient(s);
 - strength;
 - dosage form;
 - pack size;
 - shelf-life;
 - storage conditions;
 - name of supplier;
 - name of manufacturer and manufacturing site(s).

The procurement agency should have a mechanism for sharing information with other procurement agencies.

The procurement agency should have an agreement with the supplier to ensure compliance with the prequalification principles and that the products supplied are the same products as were prequalified (e.g. they are manufactured at the same site and the same processes are adhered to). The list should be reviewed and updated at regular intervals, at least every year. Newly prequalified manufacturers should be added to the list as they become qualified, and non-compliant manufacturers should be removed from the list as soon as they are recognized as such.

Where possible, more than one supplier of a product should be included on the list to ensure open and transparent procurement through competitive procurement procedures (see Module III).

II.5 Requalification and monitoring

Requalification should occur at regular intervals. Routine reinspection of manufacturers should take place at least once every three years. Routine re-evaluation of product information or questionnaires should be done every three years. Non-routine re-evaluation and/or inspection should be done when necessary, e.g. when the manufacturer implements any change to the formula, manufacturing method or manufacturing site; if any product supplied is considered not to be in compliance with the agreed specification of the product; or if a serious complaint has been received. For more details on reassessment see Module VI.

Random samples of batches of pharmaceutical product(s) supplied by prequalified manufacturers should be taken for independent testing for compliance with final product specifications as part of the continuous monitoring programme.

II.6 Monitoring of complaints

Complaints should be handled in accordance with a written procedure.

A written report of the complaint, investigation, recommendations for action where relevant, and outcome should be available to the procurement agency.

Any complaint concerning a pharmaceutical product or batch of products supplied by the manufacturer should be thoroughly investigated. The nature of the complaint should be communicated to the manufacturer.

II.7 Cost recovery

It is recommended that the costs of prequalification should be covered by the procurement agency.

If costs are to be recovered, defined transparent procedures should be established and manufacturers should be notified of these procedures in advance. Cost recovery should be based on a fee-for-services structure.

Purchasing

Introduction

Pharmaceutical products should be purchased with the aim of procuring effective, good-quality medicines at the lowest possible cost. Prequalification of products and manufacturers as described in Module II contributes to ensuring in advance that manufacturers and suppliers can deliver quality products on a sustained basis.

This module gives an overview of the strategies and methods used in pharmaceutical procurement. The term procurement in this module relates specifically to the purchase of health sector goods from manufacturers or suppliers. The module goes on to describe the key activities in purchasing pharmaceutical products, as well as the recommended organizational structure of the procurement agencies who carry out these key activities.

III.1 Strategies for health systems

Although many health systems are decentralizing, some aspects of the health system are often handled more efficiently at a central level. Approval for a list of essential pharmaceutical products and registration or licensing of pharmaceutical products are normally the responsibility of the competent authority at the national level. Centralized procurement of pharmaceutical products increases the quantity obtained under each purchase contract and usually reduces the cost of the products. Programme officials should therefore consider consolidating quality assurance procedures at the national level and pooling demands for pharmaceutical products under a common contract.

Four strategic objectives for good pharmaceutical procurement are relevant to any public sector drug supply system, whether it is managed using public or private services or a combination of both. These are as follows (12):

- selection of reliable suppliers of quality products;
- procurement of the most cost-effective pharmaceutical products in the right quantities;
- timely delivery; and
- achievement of the lowest possible *total* cost.

These objectives should be achieved through efficient and transparent management reflected in an adequate division of the different activities and responsibilities; appropriate standardization, selection, specification and quantification of pharmaceutical products; the use of good financial management procedures and competitive procurement methods; and a quality system that involves the selection and monitoring of qualified suppliers and their products.

It is recommended that a standard procedure be prepared to assist in the calculation of the lowest possible total cost. This approach aims to ensure that costs are calculated

in a consistent manner, with a consistent weight given to each of the factors taken into account.

To be effective, a procurement office should ensure that the following principles are applied.

- Prequalified products are purchased from approved manufacturers whenever possible.
- Procurement and purchasing procedures are transparent.
- Activities follow formal written procedures throughout the process, including explicit criteria for awarding contracts.
- Purchasing is based on competitive procurement methods, except for very small or emergency orders.
- Members of the purchasing groups purchase all contracted items from the suppliers who hold the contract.
- Purchasing and tender documents list all pharmaceutical products by their INN or national generic names.
- Suppliers are selected and monitored through a process that takes into account product quality, service reliability, delivery time and financial viability.
- Intellectual property rights are respected in accordance with best practice and international law.

Considerable effort has been put into the development of appropriate policies and procedures for the procurement of health sector goods (pharmaceuticals, vaccines and condoms) by the World Bank. The reference documents are the standard bidding documents (13) and the accompanying technical note (14). Although these documents are designed to meet the World Bank's specific requirements, they include much sound guidance for use by all involved in the processes of procuring health sector goods.

III.2 Procurement methods

Although there are different methods of procurement, they all involve a number of common activities that must take place beforehand. These activities are the establishment of technical specifications, quantification of requirements, issuing of some form of tender, and selection of product(s) and manufacturer(s) preferably based on prequalification.

Responses to tenders should be examined to ensure that offers have been received from invited suppliers and that the offers are substantially responsive to the terms and conditions of the tender. Awards should be made to the maker of the lowest acceptable bid that meets the terms and conditions of the tender. Disqualification of low bidders should be documented and form part of the tender record. Following a review of the adjudication by an independent panel, the companies should be informed of the outcome of the tender, and a contract should be awarded to the successful company. The contract must substantially reflect the terms and conditions detailed in the tender.

A brief description of different procurement methods is given below.

III.2.1 ***Restricted tender***

In a restricted tender, also called a “closed bid” or “selective tender”, interested suppliers are approved in advance through a prequalification process. This type of procurement is often referred to as “limited international bidding” (LIB) which is an “invitation to competitive bids” (ICB) conducted by direct invitation to all prequalified suppliers.

Procurement agencies should use restricted tenders to invite bids from prequalified suppliers for all health sector goods and services whenever possible.

III.2.2 ***Competitive negotiation***

This method is also referred to as “international/national shopping”. The basis of this method is the comparison of price quotations obtained from several local or foreign suppliers. Usually, quotations are solicited from a minimum of three suppliers to ensure competitive prices.

This method is appropriate for procuring small amounts of readily available products. However, its use should be explicitly justified, and approval should be obtained from senior management. Only prequalified suppliers should be used.

III.2.3 ***Direct procurement***

In direct procurement, products are obtained directly from a single source without applying the requirements of a tender process or comparing price quotations.

Normally direct procurement is not recommended, but it may be used when there is only one prequalified source for the product to be procured. A history of “reasonable” prices for the product in question should be assessed to negotiate the price with the supplier.

III.2.4 ***Open tender***

Open tender is the formal procedure by which all manufacturers, national and international, are invited to bid for the sale of general goods. The term “international competitive bidding” (ICB), which is an open tender to all manufacturers, is often used.

Open tendering is not appropriate for health sector goods, because it may be difficult to establish, before a contract is awarded, whether unknown bidders will be able to supply products of the required quality in the required quantities on a sustained basis.

III.3 **Quality assurance in purchasing**

The procurement agency should have a documented infrastructure for purchase and procurement of health sector goods and services, which should aim to ensure that pharmaceutical products are of the quality required for their intended use. Quality

assurance therefore incorporates GMP and other factors, some of which are outside the scope of these guidelines, such as product design and development.

III.4 Key activities in purchasing

III.4.1 *Product selection and specification*

The selection of pharmaceutical products based on a national formulary or on the essential medicines list is recommended. WHO's *Model Formulary (15)* and *Model Essential Medicines List (4)* identify the most cost-effective and affordable pharmaceutical products to treat prevailing health problems. They are updated regularly and are made freely available for adaptation by countries. The health systems of many industrialized and developing countries have used the essential medicines concept for decades to use existing resources effectively. Because the use of a national formulary reduces the number of products used, supply management activities and inventory carrying costs are minimized.

Mechanisms for procurement of non-essential pharmaceutical products by public and private health systems should be available. Procurement of such products should be explicitly justified and subject to approval by authorized officials.

Procurement and tender documents should list pharmaceutical products by their INN or national generic names.

Each product selected should be available in a dosage form which offers acceptable safety, efficacy and quality, including acceptable stability and shelf-life under the recommended storage conditions.

If two or more pharmaceutical products appear to be similar according to these criteria, the choice between them should be made after a careful evaluation of their relative efficacy, safety, quality, cost, lead-time and availability from prequalified manufacturing sites. When comparing costs of pharmaceutical products, the cost of the whole course of treatment, not only the unit cost, should be taken into consideration. The choice may also be influenced by other factors such as transportation charges, storage requirements and shelf-life.

III.4.2 *Product quantification*

All requests for products should include quantities and required delivery dates. Accurate quantification of needs is essential to avoid shortages or excess stocks. Shortages could lead to patients not being treated or being improperly treated. Excess stocks could lead to additional storage costs and expiry of products before they are used.

The possible methods of product quantification include the consumption method, the morbidity method, and the adjusted or extrapolated consumption method.

The consumption method uses records of past consumption of individual pharmaceutical products.

The morbidity method estimates the need for specific pharmaceutical products according to the incidence of common diseases, the number of patients attending health care facilities and treatment patterns for the diseases treated. Adherence to standard treatment guidelines will make treatment patterns more predictable.

The adjusted or extrapolated consumption method uses data on disease incidence and drug consumption from a standard supply system and extrapolates the utilization rate to the supply system under consideration.

The consumption method is the most reliable method provided that the consumption records are accurate, the supply pipeline has been consistently full and no major changes are anticipated in the near future. Otherwise, one of the other methods should be used to enable a more accurate quantification of procurement requirements to be made.

If sufficient data are available, the morbidity method of quantifying drug requirements can be used to detect discrepancies in past consumption patterns, which could be indicative of irrational drug use or theft of pharmaceutical products.

III.4.3 ***Selection of suppliers***

Prequalification is the procedure by which the products, manufacturers and suppliers are assessed before bids are solicited for specific products. The prequalification process for pharmaceutical products developed by WHO is based on the principles stated in Modules I and II.

Prequalification requires time. However, once a list of prequalified products and manufacturers has been prepared, adjudication and awarding of contracts can be expedited.

Postqualification is the process by which products and manufacturers are assessed after bids have been received. This process may cause delays because, if there are several offers from unknown suppliers, it will be necessary to validate the ability of these suppliers to supply products of the required quality in the required quantities before any contracts are awarded. Postqualification is therefore not recommended for pharmaceutical product procurement.

Procurement agencies should restrict tenders to prequalified products and manufacturers, soliciting bids from those manufacturers and suppliers that have been prequalified as described in Module II, or by contracting the services of a procurement agency which meets the recommended norms and standards for carrying out prequalification.

III.4.4 ***Adjudication of tenders***

The adjudication of tenders is an important step in procurement. The procedure, including the decision-making process, should be transparent and documented. Decisions taken should ensure both appropriate quality and lowest cost to the procurement agency.

Following a bid the award should be made to the supplier making the lowest offer responding fully to the bid. When considering information submitted on aspects of quality assurance, the procurement agency should seek expert advice to determine if the offer is fully responsive.

When adjudicating tenders, the attention given to the financial stability of the manufacturer should not outweigh the consideration of measures taken to ensure quality of products.

III.5 Organization and responsibilities

The key activities of purchasing pharmaceutical products (product selection and specification, quantification, prequalification and adjudication of tenders) should be performed by different people, sections or departments with the appropriate expertise and resources for performing the specific functions.

III.5.1 Procurement agency structure

The section or department responsible for purchasing pharmaceutical products in the procurement agency should have an organizational chart indicating the positions and names of the personnel responsible for the key activities, as well as the reporting lines.

Purchasing office

The purchasing office should be appropriately staffed to prepare and issue tenders, and to award, administer and monitor contracts. In addition, it should be able to ensure that information concerning product selection, specification, quantification, supplier preselection and funding is handled appropriately. This office should follow transparent, written procedures throughout the process of purchasing and should use explicit criteria for deciding to whom to award contracts.

All staff in the purchasing group must sign confidentiality agreements and declarations of conflict of interest.

Product selection office

A committee should be responsible for identifying products to be purchased from the essential medicines list or the national formulary. If such a committee does not exist, an ad hoc committee may be set up for this purpose.

Each selected product should have standard specifications, including the dosage form, pack size, acceptable shelf-life and any other information necessary (e.g. storage conditions).

Quantification office

This office should be responsible for ensuring the following.

- The quantities ordered are based on a reliable estimate of actual need.
- Procurement takes into consideration long-term contracts to achieve

economies of scale and reduce work in prequalification. This approach applies to both centralized and decentralized systems.

- Procurement takes into account the potential benefits of joining with other procurement agencies and pooling requirements.
- Products are delivered according to requested delivery dates.

Finance office

There should be mechanisms in place to ensure reliable financing for procurement. Good financial management procedures should be followed to ensure that financial resources are used with maximum efficiency.

Funds should be allocated before the tender is issued, and should be released in accordance with the purchase contract.

Quality office

Prequalification procedures should provide assurance that the pharmaceutical products purchased are of acceptable quality and meet applicable international standards as described in Module II.

Adequate laboratory services should be available to test pharmaceutical products independently according to specifications and standards. Random sampling and testing should be carried out before and after purchase.

The procurement agency (contract-giver) may decide to contract the services of an agency (contract-acceptor) with expertise in technical assessment of product data and information and/or inspection of manufacturing facilities. However, the contract-giver remains responsible for the implementation and monitoring of these activities.

Management oversight

Procurement should be planned properly, and procurement performance should be monitored regularly.

An independent committee should review adjudicated tenders. Committee members should have financial, legal and programme planning expertise and experience.

III.5.2 *Responsibilities*

Each staff member who undertakes procurement or provides support to procurement should have a job description which clearly describes his or her tasks and responsibilities. All staff must have signed confidentiality agreements and declarations of conflict of interest before they carry out any tasks related to purchasing of pharmaceutical products.

The responsibility placed upon any individual should not be more than that person can handle. There should not be any gaps or overlaps in the areas of responsibility.

III.6 Monitoring of performance of prequalified manufacturers

There should be a procedure for continuous monitoring of prequalified products and manufacturers, whether or not the manufacturer is supplying product(s).

If a decision is taken to remove a product or manufacturer from the prequalification list, the manufacturer should be notified. All recipients of the list should be informed accordingly.

Performance of manufacturers and product compliance should be monitored. Monitoring should include at least the following aspects:

- sampling and testing of samples for quality control;
- verification that the product batches supplied have been manufactured in compliance with standards and specifications accepted in the product information;
- pharmacovigilance;
- monitoring of complaints;
- reinspection of manufacturing sites;
- reassessment of product information;
- monitoring of direct and indirect product costs; and
- monitoring of adherence to delivery schedules.

The monitoring process should include continuous commercial monitoring that includes tracking of lead-time and monitoring for compliance with all of the contract terms and conditions.

In addition, the quality of the pharmaceutical products supplied should be monitored. This includes sampling and independent testing of ordered and delivered products. Tests should include at least visual examination; shelf-life; compliance with labelling, packaging and shipping instructions; and laboratory analysis when appropriate (e.g. identification or assay).

There should be an information system that keeps track of the value of contracts awarded, the value of total purchases from each supplier per year and the performance for each tender (e.g. speed of delivery and compliance with specifications).

The section or department of the procurement agency responsible for prequalification of products and manufacturers should schedule routine requalification at predetermined intervals as described in Module VI.

III.7 Patents

In evaluating product information during prequalification and during tendering, information regarding the patent status should be requested. No infringement of patents by any United Nations or other procurement agency should occur.

A person within the procurement agency should be identified as having responsibility for checking the patent status of a particular product or formulation and to recommend actions to be taken regarding the protection of intellectual property

rights for the product. This person will often be a member of the legal department of the organization.

Countries requesting products from procurement agencies should be responsible for ensuring that the products supplied comply with the destination country's legislation on registration/licensing status and patent registration or restrictions.

III.8 Donations

Any procurement agency receiving donations should handle donated drugs in accordance with a written procedure to ensure that patients receive products of known, appropriate quality.

WHO's *Guidelines for drug donations* (16) outline the key issues. The principles established in these guidelines should be followed.

Module IV

Receipt and storage of purchased products

Introduction

The procurement agency should ensure that the pharmaceutical products purchased are received and stored correctly and in compliance with applicable legislation and regulations. Products should be received and stored in such a way that their quality and integrity is preserved, batch traceability is maintained and stock can be rotated. This module focuses on quality assurance and quality control during receipt and storage of products.

Quality control is concerned with sampling, specifications and testing as well as with the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials or products are not released for use until their quality has been judged satisfactory for their intended purpose.

Each procurement agency should have access to a quality control department, which should meet the general requirements for facilities, policies and procedures, staff expertise, experience and training as specified in Module I, as well as the requirements outlined in Module II under “Analysis of samples”. The quality control department must be capable of undertaking the full range of tests required, or of managing any subcontracting of such work to third parties correctly while retaining responsibility for the quality of the work done.

The principles established in the *WHO guidelines for good storage practice* (17) (see Appendix 14) should be followed throughout the steps described in this module.

IV.1 Pre-shipment quality control

Each batch of finished product should be tested in a laboratory to determine that it conforms satisfactorily to its finished product specification, prior to supply.

In lieu of testing by the procurement agency, a certificate of analysis may be accepted from the supplier, provided that the agency establishes the reliability of the supplier’s analysis through appropriate periodic validation of the supplier’s test results and through on-site audits of the supplier’s capabilities.

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

IV.2 Receipt of stock

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

All incoming materials and finished products should be quarantined immediately after receipt until they are released for use or distribution. Imported pharmaceutical products should be quarantined until test results confirm that the products meet all of the requirements, specifications, terms and conditions of the purchase order. A review of certificates of analysis should be made to confirm that what has been delivered is what was ordered and is certified by the manufacturer to meet specifications.

Upon receipt, each incoming delivery should be checked for correspondence between the order, the delivery note and the supplier's labels. The consignment should be examined for integrity of packages and seals, and for uniformity of the containers. Should the delivery comprise more than one batch, it should be subdivided according to the supplier's batch number. Containers should be cleaned where necessary and labelled, if required, with the prescribed data, e.g. label description, batch number, type and quantity. Each container should be carefully inspected for possible contamination, tampering and damage, and any suspect containers or the entire delivery should be quarantined. Damage to containers and any other problem that might adversely affect the quality of the material should be recorded and investigated.

The person responsible for receiving the goods should be independent of the person responsible for purchasing the goods.

IV.3 Postprocurement quality control

IV.3.1 *Sampling*

The procedures for receipt of supplies should include random sampling for independent laboratory analysis to ensure that pharmaceutical products meet the required standards. Sampling should be performed in accordance with a written procedure. Products may also be randomly sampled at the end of the distribution chain and sent for independent analysis. Representative samples should be taken from containers in the consignment. The samples should be analysed for compliance with the product specification.

Samples should be taken only by appropriately trained and qualified personnel and strictly in accordance with written sampling instructions. Containers from which samples have been taken should be labelled accordingly.

Following sampling goods should be quarantined. Batch segregation should be maintained during quarantine and all subsequent storage. Materials and pharmaceutical products should remain in quarantine until an authorized release or rejection is obtained.

IV.3.2 *Rejected materials*

Stringent precautions should be taken to ensure that rejected materials and pharmaceutical products cannot be used. Rejected goods should be clearly marked as such and stored separately from other materials and pharmaceutical products in a

locked compound accessible only to authorized and trained responsible personnel, while the materials await destruction or return to the supplier. Whatever action is taken should be approved by authorized personnel and recorded. Rejected materials should be handled in accordance with a written procedure.

IV.4 Storage of materials and products

IV.4.1 Staff

All members of staff should be trained to observe high levels of personal hygiene and sanitation. The duties and responsibilities of all members of staff should be available in the form of a written job description.

Personnel employed in storage areas should wear protective or working garments appropriate for the activities they perform.

IV.4.2 Storage areas

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products, including segregation of rejected, expired, recalled or returned stock.

Adequate ventilation should be in place to control temperature and relative humidity. Where special storage conditions are required (e.g. temperature and humidity) these should be provided, checked and monitored.

Precautions should be taken to prevent unauthorized entry into the storage areas.

A written procedure for fire control measures should be in place, including prevention of fire, fire detection measures and fire drills. Fire detection and fire-fighting equipment should be serviced regularly. Smoking should not be permitted in the storage areas.

IV.4.3 Storage conditions

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 according to the first-in, first-out rule.

Stock should be stored off the floor and suitably spaced to permit cleaning and inspection. Pallets should be kept in a good state of cleanliness and repair.

Storage areas should be kept clean and free of vermin and accumulated waste. A written sanitation programme should be available indicating the cleaning and pest-control methods used, and their frequency of use. Safe pest-control agents should be used which will not contaminate materials and pharmaceutical products. There should be appropriate procedures for the cleaning up of any spillage to eliminate any risk of contamination.

Storage conditions used for pharmaceutical products and materials should comply with the instructions on the label which are based on the results of stability testing.

In general, the instructions on the label have the meanings given in Table 1.

Table 1

Meaning of storage instructions given on the labels of pharmaceutical products

On the label	Means:
Do not store over 30 °C	From +2 °C to +30 °C
Do not store over 25 °C	From +2 °C to +25 °C
Do not store over 15 °C	From +2 °C to +15 °C
Do not store over 8 °C	From +2 °C to +8 °C
Do not store below 8 °C	From +8 °C to +25 °C
Protect from moisture	No more than 60% relative humidity under normal storage conditions; to be provided to the patient in a moisture-resistant container
Protect from light	To be kept in a light-resistant container

In certain cases, e.g. with freeze-sensitive vaccines, products that have been stored below the temperature specified on the label should be destroyed. Freeze-sensitive products should be equipped with a “freeze-watch” monitoring device.

Monitoring of storage conditions

The equipment used for monitoring should be calibrated at suitable predetermined intervals and the results should be recorded and retained. All monitoring records should be kept for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation. Temperature mapping of the facility should be well designed to support assurance of uniformity of the temperature across the storage facility. It is recommended that temperature monitors should be placed in the worst-case areas of the facility. Recorded temperature monitoring data should be available for review.

Equipment used for monitoring should be calibrated at defined intervals.

IV.4.4 *Labelling and containers*

All materials and pharmaceutical products should be stored in containers which do not adversely affect the quality of the material or products, and which offer adequate protection from external influences, including bacterial contamination in some circumstances.

All containers should be clearly labelled with at least the name of the material or product, the batch number, the expiry date or retest date, the specified storage conditions and reference to the relevant pharmacopoeia where applicable. Only authorized abbreviations, names or codes should be used.

IV.4.5 *Miscellaneous and hazardous materials*

Materials which may affect other materials stored in their vicinity should be handled in accordance with a written procedure. Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products. Toxic substances and flammable materials should be clearly marked as such and should be stored in suitably designed, separate, enclosed areas as required by national legislation. Flammable substances should be kept away from corrosive or oxidant substances at all times.

IV.4.6 *Stock control*

Stock rotation and control is best maintained by the use of a proprietary stock control system. Care must be taken to select a system that can manage the rigid requirements for batch number control and expiry dating which are essential for handling pharmaceutical products. Many commercial systems lack these features. In case of doubt advice should be sought from competent experienced personnel.

Periodic stock reconciliation should be performed comparing actual and recorded stock levels.

All significant stock discrepancies should be subjected to investigation as a check against inadvertent mix-ups and/or incorrect issue.

In manufacturing facilities, partly used containers of materials and pharmaceutical products should be securely reclosed and resealed to prevent spoilage and/or contamination during subsequent storage. Materials and pharmaceutical products from containers which are open or partly used should be used up before a new container is opened.

Damaged containers should not be issued unless it is certain that the quality of the material inside is unaffected. Where possible, damaged containers should be brought to the attention of the person responsible for quality control. Any action taken should be documented.

Control of obsolete and outdated materials and products

All stock should be checked regularly for obsolete and outdated materials and pharmaceutical products. All due precautions should be observed to prevent issue of outdated materials and pharmaceutical products. The handling of such materials should be subject to a written procedure.

Recalled materials

Recalled materials should be handled in accordance with a written procedure. Written records of all major actions with the signatures of the person responsible for carrying out each action should be maintained.

Recalled products should be identified and stored separately in a secure area until

a decision has been taken on their fate. The decision should be made as soon as possible. An assessment may be made only by an appropriately qualified and experienced member of staff.

Returned goods

Returned goods should be handled in accordance with a written procedure. They should be placed in quarantine until a decision has been taken on their fate. Products returned from the market should be destroyed unless it is certain that their quality is satisfactory. In that case, they may be considered for resale. The nature of the product, any special storage requirements, 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 recorded.

Waste materials

Waste materials should be handled in accordance with a written procedure. 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.

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.

IV.4.7 *Documentation: written instructions and records*

Written instructions and records should be kept which describe the storage procedures and define the routes of materials, pharmaceutical products and information through the procurement agency, including handling of expired stock. Batch traceability is essential in the event of a product recall.

Permanent information, written or electronic, should exist for each stored material or product to indicate recommended storage conditions, any precautions to be observed and retest dates. Pharmacopoeial requirements and other current national regulations concerning labels and containers should be respected at all times.

Records should be retained for each delivery. They should include the description of the goods, quality, quantity, supplier, supplier's batch number, the date of receipt, assigned batch number and the expiry date. National regulations which state a period for retention of records must be observed. Where no such regulations exist, records should be retained for one year after the end of the shelf-life of incoming products.

Comprehensive records should be maintained of all receipts and issues of materials and pharmaceutical products according to a specified system, e.g. by batch number.

Module V

Distribution

Introduction

A well-managed distribution system should achieve the following objectives (1).

- Maintain a constant supply of drugs.
- Keep drugs in good condition throughout the distribution process.
- Minimize drug losses due to spoilage and expiry.
- Maintain accurate inventory records.
- Rationalize drug storage points.
- Use available transportation resources as efficiently as possible.
- Reduce theft and fraud.
- Provide information for forecasting drug needs.

This module focuses on measures to be taken to ensure product integrity and quality during distribution, and outlines the main points. The principles established in the WHO *guidelines for good trade and distribution practice (18)* (see Appendix 15) should be followed.

V.1 Transport conditions

Materials and pharmaceutical products should be transported in such a way that the integrity of the material or pharmaceutical product is not adversely affected and that appropriate storage conditions are maintained.

Every precaution should be taken to minimize the risk of theft and fraud.

V.2 Cold chain

Special care should be exercised when using dry ice in cold chains. In addition to addressing safety concerns, it is necessary to ensure that the material or product does not come in contact with the dry ice, as this may adversely affect the quality of the product, e.g. as a result of freezing.

V.3 Temperature monitoring and records

Where appropriate, the use of devices to monitor conditions such as temperature during transportation is recommended. Records should be available for review.

V.4 Delivery order

The dispatch and transport of materials and pharmaceutical products should be carried out only after receipt of a delivery order, which has to be documented. There should be a procedure to ensure that products are supplied to authorized recipients only.

V.5 Dispatch procedures and policies

Rules for dispatch procedures should be established according to the nature of the materials and pharmaceutical products being dispatched and after taking into account any special precautions to be observed. Any special packaging requirements for movement of goods must be met. Some goods may require special protection before they can be shipped by boat or by air. All legislation that may affect these requirements must be fulfilled.

V.6 Dispatch containers

The outside container should offer adequate protection from all external influences and should be indelibly and clearly labelled.

Products should be packed in such a way as to minimize the risk of theft, e.g. by using locked containers or by shrink-wrapping entire pallets in plastic.

V.7 Dispatch records

Records for dispatch should be retained, stating at least the following:

- date of dispatch;
- customer's name and address;
- product description, e.g. name, dosage form and strength (if appropriate), batch number and quantity; and
- transport and storage conditions.

V.8 Traceability

Records of distribution should contain sufficient information to enable traceability of the product from the point of supply to the end user.

Traceability of goods is crucial in case of the need for product recalls. It will also help to detect theft and fraud. Any discrepancies should be investigated and followed up by appropriate measures to tackle possible security breaches.

V.9 Port of entry

All conditions required for storage should be achievable at the port of entry of goods. This is particularly important for all temperature-sensitive products shipped to ports where temperatures may be less well controlled. Specific arrangements may need to be made with local handling agents and customs to ensure speedy handling and clearance.

Security measures to prevent theft, fraud and bribery should be in place during storage at the port of entry.

V.10 Packaging of products and materials

If any packaging or repackaging is required because of breakages, all the policies and procedures described in WHO GMP guidelines (3) should be followed in their entirety.

Module VI

Reassessment

Introduction

The quality of all products and services procured in accordance with this Model should be continuously monitored. Reassessment will be required to ensure that the products procured continue to meet the norms and standards defined. This module briefly outlines the principles of routine and non-routine assessment of manufacturers, products and contracted-out services.

VI.1 Re-evaluation of manufacturers

Re-inspection of manufacturers should take place at regular intervals at least every three years.

Manufacturers should inform the procurement agency immediately of any changes to the manufacturing site or equipment that may have an impact on its prequalification.

Non-routine requalification may be required in the following situations:

- in case of any omission of information in the initial assessment;
- if false or misleading information is suspected during the follow-up assessment;
- if changes are implemented that may have an impact on the prequalification of the manufacturing site, such as changes to key personnel or organizational structure, changes to equipment, apparatus or the manufacturing process, or the renovation or addition of facilities that need validation, commissioning or re-inspection; or
- if a complaint considered to be serious in nature has been received.

The procurement agency should suspend or withdraw a prequalified facility from the prequalification list if there is evidence of non-compliance with the requirements for prequalification.

VI.2 Re-evaluation of products

Product information should be reviewed every three years, or sooner if major changes occur in the meantime.

Under routine circumstances there will be no requirement for the manufacturer to retest the product as part of the re-evaluation process. However, circumstances may arise in which retesting is necessary.

Manufacturers should inform the procurement agency of any contemplated changes to the product that may affect its safety, performance, efficacy or quality. With regard to the product, manufacturers should for instance report the following changes:

- change of manufacturing process, site or equipment relating to the product;

- change of contract manufacturers;
- change of pharmaceutical product release control laboratories;
- changed suppliers of starting materials or container or closure;
- changes to the formulation or composition of the product;
- new analytical method in the testing of starting material, intermediate or final product; or
- change of specifications.

Sufficient time must be allowed for the necessary testing, e.g. stability testing or bioequivalence testing. Based on the information submitted, the person responsible for prequalification should decide whether to approve the changes or whether to request additional data which demonstrate the equivalence of the product to the one that has been prequalified.

The section or department responsible for prequalification of products and manufacturers should inform the purchasing office about the changes and the result of the evaluation of such changes.

Non-routine re-evaluation of products should be done in the following cases.

- If any omission by the manufacturer in the initial evaluation procedure, or during the follow-up activities, is evident in relation to the requirements, including compliance with quality system standards and failure to notify complaints.
- If any batch or batches of supplied product(s) are documented by the procurement agency not to be in compliance with the agreed specifications of the product or to reveal failure(s) regarding safety, performance or quality of the device.
- If the investigation of a complaint considered leads to the conclusion that the quality and/or safety of the product is in question.
- If any fraud or misconduct by the manufacturer is evident.
- If any batch or batches of product(s) was supplied and is considered not to be in compliance with the agreed specification of the product.
- If a complaint considered to be serious in nature had been received by the organization.
- In cases of changes or variations to products, the WHO guidelines *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for drug regulatory authorities* (6) give guidance on when to proceed with which type of re-evaluation.
- If, in the opinion of the organization, changes made in the sourcing of the API, formulation, manufacturing method, facility or other production aspects require that a reassessment be made.
- If supply has been suspended for one year or longer.

VI.3 Monitoring of contracted-out services

VI.3.1 ***Storage and distribution***

Monitoring of the performance of contractors and follow-up of non-compliance

should be carried out according to a written procedure. It should include continuous monitoring, as well as periodic review and renewal of the contract.

Continuous monitoring should include tracking of cost, order and delivery status, lead-time and compliance with contract terms and conditions. A management information system should be in place for this purpose. There should be continuous quality control of pharmaceutical products supplied including random sampling and a procedure for dealing with complaints. The procurement agency should document any reported problems with quality control or service and inform the contractor of each problem. Continuous monitoring should also include compliance of the contract-giver with contract conditions, and correction of any factors that prevent the contract-acceptor from fulfilling the specified duties.

Periodic review of the contract should be based on an assessment of the contractor's overall performance. The criteria outlined for monitoring of prequalified products and manufacturers (see Section III.6) also apply to monitoring of contract-acceptors who store and distribute pharmaceutical products.

VI.3.2 ***Quality control laboratories***

Contracted laboratories should comply with the principles of good laboratory practice (GLP) (19). The accreditation status alone does not guarantee compliance with GLP. The performance of contracted laboratories should be continuously monitored.

VI.3.3 ***Contract research organizations***

Contract research organizations (CROs) should be inspected as part of the assessment process to verify that raw data correspond to submitted data, and to assess compliance with standards during the conduct of clinical and bioequivalence studies. Monitoring and requalification should ensure that the principles of good clinical practices (GCP) (20), good practices for quality control laboratories (10) and GLP (19) are adhered to.

Conclusion

A trend towards the introduction of quality systems principles in the internal operations of organizations concerned with pharmaceutical quality assurance has led to the publication of the WHO document *Quality systems requirements for national good manufacturing practice inspectorates* (21), which outlines principles for implementing a quality management system (see Appendix 16). The quality management principles described are valid for all key aspects of procurement and have been considered in designing and testing the model quality assurance system presented in this document. It is recommended that procurement agencies implement this Model to ensure a harmonized approach to quality assurance in all key activities of procurement.

The establishment and operation of a quality system is an essential element in the mutual recognition of the outcomes of prequalification activities. Once a harmonized

system is in place, agencies will be able to exchange information on assessment of product information and inspection findings.

Sharing this information will eliminate the need for duplication of prequalification procedures. Reliance on a harmonized system for the procurement of products meeting predefined norms and standards will expedite procedures for obtaining quality products at competitive prices. The benefit will be greatest for those medicines for which demand is high, e.g. medicines for priority diseases affecting a large part of the world's population in areas where drug regulatory capacities and health budgets are limited.

References

1. Quick JD, et al. (eds). *Managing drug supply*. 2nd ed. revised and expanded. Hartford, CT, Kumarian Press, 1997.
2. *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials*. Volume 1. Geneva, World Health Organization, 1997.
3. *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials*. Volume 2, updated edition. Good manufacturing practices and inspection. Geneva, World Health Organization, 2004.
4. *14th Model List of Essential Medicines*. Geneva, World Health Organization, 2005 (http://www.who.int/medicines/organization/par/edl/expcom13/eml13_en.pdf).
5. Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 8 (<http://www.who.int/medicines/qsm/trs908/trs908.pdf>).
6. *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for drug regulatory authorities*. Geneva, World Health Organization, 1998 (WHO/DMP/RGS/98.5).
7. Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant. In: *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for drug regulatory authorities*. Geneva, World Health Organization, 1998, Annex 6 (WHO/DMP/RGS/98.5) (http://mednet3.who.int/prequal/documents/WHO_DMP_RGS_98_5_R.pdf).
8. *WHO Certification scheme on the quality of pharmaceutical products moving in international commerce*. Geneva, World Health Organization, 2000 (WHO/EDM/QSM/2000.2) (<http://www.who.int/medicines/organization/qsm/activities/drugregul/certification/certifscheme.shtml>).
9. *Guide for a quality systems manual in a control laboratory*. Geneva, World Health Organization, 1998 (WHO/VSQ/98.04) (<http://www.who.int/vaccines-documents/DocsPDF/www9840.pdf>).
10. Good practices for national pharmaceutical control laboratories. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 3.
11. Guidance on Good Manufacturing Practices (GMP): inspection report. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 6.
12. *Operational principles for good pharmaceutical procurement*. Geneva, World Health Organization, 1999 (WHO/EDM/PAR/99.5).
13. *Standard bidding documents. Procurement of health sector goods (pharmaceuticals, vaccines, and condoms)*. Washington, DC, World Bank, 2000 (revised February 2001, March 2002 and March 2003) (<http://siteresources.worldbank.org/PROCUREMENT/Resources/health-ev4.pdf>).
14. *Technical note. Procurement of health sector goods*. Washington, DC, World Bank, 2000 (<http://siteresources.worldbank.org/INTPROCUREMENT/Resources/health-tn-ev2-a4.doc>).

15. *Model formulary 2004*. Geneva, World Health Organization, 2004 (<http://www.who.int/medicines/organization/par/formulary.shtml>).
16. *Guidelines for drug donations*. Geneva, World Health Organization, 1999 (WHO/EDM/PAR/99.4).
17. Guide to good storage practices for pharmaceuticals. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908). Annex 9 (http://www.who.int/medicines/library/qsm/good_storage.pdf).
18. Good trade and distribution practices for pharmaceutical starting materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-eighth report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 917), Annex 2 (http://www.who.int/medicines/strategy/quality_safety/tr917ann2.pdf).
19. Handbook. *Good laboratory practice (GLP)*. Quality practices for regulated non-clinical research and development. Geneva, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), 2001 (TDR/PRD/GLP/01.2).
20. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: *WHO Expert Committee on the Use of Essential Drugs, Sixth report*. Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850), Annex 3.
21. Quality systems requirements for national good manufacturing practice inspectorates. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 8.

Appendix 1

Example of a Code of Conduct

1. Introduction

This Code of Conduct must be followed by appointed staff members as well as all other staff involved.

All members of staff including temporary advisers and experts appointed to carry out evaluations and inspection on behalf of WHO should keep in mind at all times the image of WHO.

(In the context of this Code of Conduct, staff and members of staff include contract appointments, short-term staff, advisers and experts appointed for the performance of work.)

2. Key responsibilities

Each member of staff, expert and temporary adviser has key responsibilities to fulfil. The overall objective is to perform these key responsibilities within the framework of this Code of Conduct.

An internal oversight framework has existed within WHO since the early days of the Organization. It is necessary periodically to ensure that all staff understand this function. The WHO summary statement on WHO's Office of Internal Audit and Oversight (IAO) which describes its purpose, authority and scope of work, should be read by each member of staff. This document summarizes the expectations for IAO and it furnishes direction for internal audit at WHO.

By accepting appointment, staff members pledge themselves to discharge their functions and to regulate their conduct to serve the best interests of WHO.

In the performance of their duties staff members shall neither seek nor accept instructions from any government or from any other authority external to the Organization.

No staff member shall accept, hold or engage in any office or occupation, which is incompatible with the proper discharge of his duties with WHO.

Staff members shall conduct themselves at all times in a manner compatible with their status as international civil servants.

Staff shall avoid any action and in particular any kind of public pronouncement which may adversely reflect on their status. While they are not expected to give up their national sentiments or their political and religious convictions, they shall at all times bear in mind the reserve and tact incumbent upon them by reason of their international status.

Staff members shall exercise the utmost discretion in regard to all matters of official business. They shall not communicate to any person any information known to them by reason of their official position, which has not been made public, except in the course of their duties or by authorization of the Director-General. At no time shall they in any way use to private advantage information known to them by reason of their official position. These obligations do not cease with separation from service.

Any staff member who becomes a candidate for a public office of a political character shall resign from the Secretariat.

The immunities and privileges attaching to WHO by virtue of Article 67 of the Constitution are conferred in the interests of the Organization. These privileges and immunities furnish no excuse to staff members for non-performance of their private obligations or failure to observe laws and police regulations. The decision whether to waive any privileges or immunities of the staff in any case that arises shall rest with the Director-General.

All staff members shall subscribe to the oath or declaration as set out in WHO Staff Regulations.

A staff member may not act as a delegate or observer for, or adviser to, his or her government.

A staff member may participate in international or national societies when such participation is not in conflict with the standards referred to in WHO Staff Rules and may represent such societies at an international meeting with the Director-General's authorization.

A staff member shall obtain the Director-General's permission before publishing articles whose contents reflect work performed for the Organization or information obtained arising out of such work.

All rights, including title, copyright and patent rights, in any work or invention produced or developed by a staff member as part of his official duties shall be vested in the Organization.

“Misconduct” means:

- any improper action by a staff member in his official capacity;
- any conduct by a staff member, unconnected with his official duties, tending to bring the Organization into public discredit; and
- any improper use or attempt to make use of his or her position as an official for his or her personal advantage.

Any conduct contrary to the terms of his oath or declaration.

2.1 **Personal responsibilities**

Staff members must be committed to a strong oversight environment and must give IAO their full cooperation.

Staff must observe, implement and maintain the responsibilities in relation to the position in which they have been appointed.

Staff must perform the work they have been allocated to the best of their ability and finalize tasks in accordance with the timeframes set by WHO.

2.2 Safety

Safety is the responsibility of WHO staff, supervisors and WHO management. It includes reporting of possible hazards and suspected hazards and taking the necessary precautions and implementing safeguards to minimize safety problems.

Staff involved in activities where safety problems may arise, e.g. the inspection of a manufacturing site, should observe safety rules and regulations as recommended by WHO, the manufacturer and national legislation.

Staff must wear protective devices such as protective clothing, shields, eye covers (glasses), earplugs, where relevant, to protect the body, organs and extremities from possible harm. Staff must use their professional knowledge to ensure that they take appropriate care of their own safety. This means that should a manufacturer not provide what is deemed to be adequate personal protection, then the inspectors should refuse to enter an area on the grounds of lack of safety.

Staff must observe national regulations when driving vehicles.

Staff must be aware of, and take, the necessary precautions when collecting samples.

Special attention to safety requirements is necessary when performing site inspections. These include aspects in relation to the dosage form and activities observed (e.g. radioactive pharmaceuticals, hazardous materials, laboratory reagents, equipment and apparatus, explosions, personnel lifts, ladders, glassware, freezers, steam, radiation, microbiological hazards, viral and biological products and waste, and other relevant possible hazards).

3. Professional competence

3.1 Qualifications and experience

The staff appointed must have the required qualifications and experience to perform the tasks required. Any person appointed to perform work for or on behalf of WHO must indicate if he/she is not suitably qualified to perform the task, or does not have the relevant experience, before taking on the work or being appointed.

When people are approached to perform work on behalf of WHO, they must be truthful in providing evidence of their qualifications and experience.

Staff must not mislead WHO or procurement agencies in relation to their qualifications and/or experience. Any case of misrepresentation of qualifications

or experience will be treated as fraud and may eventually lead to prosecution. No future employment in any capacity by any WHO or United Nations organization will be possible at any time.

4. **Conduct**

During daily activities, staff must maintain high standards of ethical conduct.

Staff must observe the WHO constitution and are responsible for complying with the WHO regulations and guidelines.

4.1 **Integrity and attitude**

To ensure that the business of WHO is conducted effectively, and without improper influence, all staff members must be persons of integrity and observe the highest standards of conduct.

- WHO must be able to rely upon staff to do the right things.
- Staff must be honest and dependable.
- Staff must be devoted to accuracy, truthfulness, objectiveness and fairness.
- Staff must not use restricted information not available to the general public for gain or to advance private interests.
- Staff must report findings such as presentation of false, misleading and fraudulent information provided to WHO.
- Staff should maintain a positive attitude towards WHO and its policies and projects.
- Staff must be dignified, diplomatic, tactful and courteous. Strong-arm tactics must be avoided.
- Staff must not act with an air of superiority or special authority.
- Staff must use a firm approach when requesting necessary and authorized information.
- Staff members are the contact persons of WHO and their action will be the basis upon which the public will judge the organization. Staff must exhibit exemplary behaviour at all times.

A staff member who has any financial interest in any business concern with which he may be required, directly or indirectly, to have official dealings on behalf of the procurement agency shall report such interests to the Director-General, who shall decide on the applicability of Staff Regulations. Staff may not have financial interests in companies to be evaluated or inspected. Shareholdings through pension schemes and other such “arm’s length” arrangements will not normally be taken as a financial interest in this context. Any doubts on this matter should be referred to the WHO Internal Audit Office for clarification.

4.2 **Attire, health and hygiene**

Good public relations require that all members of staff dress appropriately for the activities to be performed. Staff should observe WHO guidelines regarding appropriate dress code.

Staff should normally wear protective clothing for inspections. Inspectors must wear protective clothing at least equivalent to that worn by employees of manufacturing sites (e.g. head covering or masks, when appropriate). Staff should conform to company procedures at all times. However, if company procedures are considered inappropriate then this fact should be recorded.

Staff involved in inspections must inform supervisors or managers of their health status when this could have impact on inspections, as persons with communicable diseases, wounds and open lesions may not be allowed in areas where products and material are exposed.

Staff are responsible for taking the necessary precautions when travelling (e.g. having the appropriate inoculations).

Staff must practice good hygiene at all times.

4.3 Gifts, meals and favours

No staff member shall accept any honour, decoration, favour, gift or remuneration from any government, or from any other source external to the Organization, if such acceptance is incompatible with his status as an international civil servant.

A staff member who is offered any honour, decoration or gift from sources external to the Organization shall report this offer to the Director-General who shall decide on the applicability of Staff Regulations.

No member of staff shall receive or accept anything of value from any manufacturer for or because of any official act that has been performed or is to be performed.

Staff will not solicit or accept directly or indirectly any gift, gratuity, favour, entertainment loan or any other item of monetary value from members of the public with whom staff members have official relationships.

When performing inspections, staff must pay for their own meals whenever possible and must make an effort to pay for their own meals even when invited by the manufacturer, unless the situation is such that it will provoke a scene or create an embarrassment to WHO.

4.4 Management relationship

Staff must promote a positive relationship with supervisors and managers.

4.5 Standard operating procedures

Staff must follow authorized standard operating procedures (SOPs) for the performance of tasks.

4.6 Travel and accommodation

Staff must observe WHO regulations, guidelines and SOPs when travelling. The relevant procedures shall be followed for planning of visits, meetings, inspections and other activities such as making reservations and paying for accommodation.

4.7 Confidentiality and conflict of interest

Staff must observe the WHO policy, country rules and regulations, and company policy with respect to confidentiality.

Staff must sign and abide by the conflict of interest and confidentiality undertaking.

4.8 Documentation and records

Staff shall follow SOPs and maintain appropriate records as required in the procedures.

All information provided by staff members must be truthful and correct, including reports and related documentation.

4.9 Contracts and terms of reference

Staff shall perform activities as stipulated in the contract or agreement for performance of work (APW) and terms of reference (TOR).

4.10 Product files, evaluation and inspection

Staff shall handle product files with care and treat all information as confidential relating to the task to be performed.

All data submitted initially and as a result of the evaluation, shall be dealt with in accordance with SOPs and be considered as confidential information between WHO and the manufacturer. All aspects relating to the inspection performed shall be considered as confidential between WHO and the manufacturer.

Staff members shall observe the requirements and undertaking with regard to confidentiality and conflict of interest.

4.11 Samples

Samples taken during inspections shall be in accordance with a WHO SOP, with the approval of the manufacturer.

4.12 Evaluation and inspection reports

There shall be written evaluation and inspection reports for every product evaluated, and every manufacturing site inspected.

The reports shall be a true reflection of the findings of the evaluation and inspection.

4.13 Provision of information and advice

Staff shall not act as consultants to individual companies or manufacturers when appointed for the purposes of evaluation or inspection for a particular project, where the company can in particular benefit from such advice, unless the information is in the public domain or given to all manufacturers.

Appendix 2

Example of a guideline on confidentiality

The evaluators and inspectors will treat all information submitted and observed during the inspections and otherwise in connection with the discharge of their responsibilities with regard to the above-mentioned project, as strictly confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below and those contained in the attached provisions for team members participating in site visits within the scope of the prequalification procedure of pharmaceutical products. An example of a confidentiality undertaking is shown at the end of Appendix 3.

Evaluators and inspectors will take all reasonable measures to ensure:

- that the confidential information is not used for any purpose other than the evaluation activities described in this document; and
- that confidential information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Evaluators and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of WHO (including by manufacturers); or
- was in the public domain at the time of disclosure by or on behalf of WHO (including by manufacturers); or
- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

All personnel involved in prequalification and related matters, having access to confidential information regarding products and manufacturers, should treat all information submitted and observed during the inspections and otherwise in connection with the discharge of their responsibilities with regard to these activities, as strictly confidential and proprietary to the procurement agency or the parties collaborating with the procurement agency.

Appendix 3

Example of a guideline on conflict of interest

Introduction

This document presents policy on “conflict of interest” as it applies to external evaluators and members of advisory committees. These two categories are together referred to as “consultants” for the purposes of these guidelines. An example of a signed statement on conflict of interest is shown at the end of this Appendix.

Definitions and principles

The common meaning of “conflict of interest” is a conflict between an individual’s private or personal interest and his or her duty. However, it may also refer to a situation where an individual has several duties which conflict without involvement of any private or personal interests.

A conflicting private or personal interest may be financial or non-financial as explained below.

When a decision-maker or consultant has a direct financial interest, however slight, in the matter to be decided, there is a conclusive presumption of bias and the decision-maker or consultant will thus be disqualified from acting.

Where a decision-maker or consultant has a non-financial interest, which gives rise to a reasonable presumption of bias, the decision-maker or consultant will be disqualified from acting. The test here is whether a reasonable observer would suspect that there is a possibility of bias, not whether that bias actually exists. A relevant non-financial interest may arise, for example, out of personal or family involvement between a decision-maker or consultant and a party whose interests are affected by the decision or recommendations. Such an interest may also arise where a decision-maker or consultant is seen to have prejudged the issues, either through preconceived opinions or prior involvement with the facts of a case on which he or she is required to make a decision on recommendations.

Conflict of interest in relation to consultants

There are a variety of situations in which consultants may find themselves in a situation of conflict of interest between their professional activities (e.g. preparation of objective and independent evaluations or membership of independent committees) and personal and private interest (e.g. private consultancies, grants to cover travel and accommodation at company-sponsored conferences, share holdings, research grants or honoraria). It is recognized that almost all consultants have some potential conflict of interest because of their present or past association with the pharmaceutical industry.

Some situations of conflict of interest are clear-cut and some are more difficult to determine. If an individual is an employee of, or a retained consultant to, a pharmaceutical company, there is a clear possibility of conflict of interest. If an individual is an employee of a government organization, does no work on behalf of pharmaceutical companies, and is not in receipt of gratuities or funding, there is a minimal risk. Between these two situations is a spectrum of possibilities where the decision as to whether there is a conflict of interest may be less obvious.

Contracts are unlikely to be offered to consultants in any one of categories 1 to 6 listed below.

1. The consultant works in the pharmaceutical industry, either as an employee or as an owner or part owner (e.g. shareholder in the pharmaceutical company to be assessed).
2. The consultant receives a retainer (fee) from one or more of the pharmaceutical companies whose products she or he has to assess or which the new product is likely to replace.
3. The consultants have a *significant* direct current relationship with one or more companies. This may take the form of (a) financial support for a current research project or projects; (b) sponsorship of graduate or postgraduate students; or (c) company employees who are under the direct responsibility of the consultant.
4. He or she receives *substantial* financial assistance or expensive equipment to conduct research on behalf of the pharmaceutical company.
5. The consultant acts or has acted as a consultant for a pharmaceutical company *on the product she or he has agreed to assess*. Such a consultancy may include sponsorship as a speaker, or appointment as chairperson at professional meetings concerning the product, or attendance on behalf of the sponsoring company at national or international professional meetings concerning the product.
6. The consultant has provided significant input to the planning or conduct of a clinical trial of the product to be assessed, for example as a principal investigator, signatory to the study report, or author of any published or unpublished paper or other report of the study. Participation limited to the inclusion of patients in a large-scale multicentre study is *not* considered a significant conflict of interest.

A conflict of interest is less likely to be seen in situations 7 to 10 (see below).

7. The consultant has occasional contracts with one or more companies for particular projects, but does not have a significant relationship with any one company. She or he has not been directly involved with the product in question.
8. The consultant owns or works for a consultancy, which does not provide advice to the pharmaceutical industry but may provide advice to other industries, such as the devices, food or paint industries. However it is unlikely that such consultants will have the technical knowledge or experience to qualify as a consultant in the pharmaceuticals field.
9. The consultant occasionally provides advice to one or more companies on the design of clinical trials to be conducted prior to submission of an application for

marketing authorization, but does not have a significant current relationship with any one company (e.g. points 1 to 6 above).

10. The consultant has been invited to attend and contribute to national or international meetings organized by professional or academic associations.

The responsibility of consultants

A drug regulatory authority cannot be aware of all of the consultant's involvements and their ramifications when a contract is offered. The onus is therefore on the consultant to declare in writing any potential conflict or what may be seen as a potential conflict to the staff member of the drug regulatory authority who negotiated the contract or committee membership. If there is any doubt, the potential conflict must be declared. The consultant may only proceed with the evaluation of the data or take up committee membership after any potential conflict has been discussed with the drug regulatory authority and found not to be significant.

For this reason, each evaluation contract requires the evaluator to sign a statement to the effect that she or he has no current conflict of interest and that, if the risk of such a conflict arises during the evaluation, the drug regulatory authority will be notified immediately in writing.

The evaluator is expected to cease reading the application *immediately she or he becomes aware of a conflict of interest*, and return it promptly to the drug regulatory authority. This clause applies also to those involved in the inspection of facilities.

Confidentiality

Any data concerning a company's product which are supplied by the drug regulatory authority to a consultant for review are strictly confidential. As stated in the contract, all materials related to or referred to in the contract must be accepted in strict confidence and held in safe and secure custody at all times. An application may be discussed only with the staff members of the drug regulatory authority.

Consultants must be aware of and avoid the possibility of indirect breaches of confidence. There is clearly a potential, consciously or subconsciously, to misuse information gained from a consultancy in other papers or scientific presentations on the product in question. Such a case would also constitute a conflict of interest. The consultant must not use information gained in this way in future scientific papers or presentations without the agreement of the company or individual that submitted the data.

Impartiality

To protect impartiality, the company concerned is not informed by the drug regulatory authority of the identity of the consultant to whom applications, data or committee papers are forwarded. For this reason, the consultant should have no direct communication with the company concerning the product. The consultant may not

disclose his or her role to the company, even after a decision on the application has been completed. This is clearly not possible in the case of an inspector of the manufacturing facility.

Subcontracting the evaluation

A consultant is not allowed to subcontract part or all of an evaluation to any second person without written permission from the drug regulatory authority. If the drug regulatory authority agrees to such an arrangement, the consultant must ensure that the subcontractor is fully aware of the provisions on conflict of interest, confidentiality and impartiality set out in these notes.

If any part of an evaluation is subcontracted, the person who actually undertakes the work must also sign all the reports to which she or he has contributed.

Example of a confidentiality undertaking and declaration of Conflict of Interest



**World Health
Organization**

PROVISIONS FOR EVALUATORS OF PRODUCT INFORMATION AND FOR INSPECTORS (TEAM MEMBER PARTICIPATING IN SITE VISITS) WITHIN THE SCOPE OF THE QUALITY ASSESSMENT PROCEDURE OF PHARMACEUTICAL PRODUCTS

In the course of discharging your functions as an expert adviser to WHO under the attached agreement for performance of work (APW), you will gain access to certain information, which is proprietary to WHO or entities collaborating with WHO, including the manufacturers of the product(s) which need to be assessed as part of the quality assessment procedure by WHO. You undertake to treat such information (hereinafter referred to as “the Information”) as confidential and proprietary to WHO or the aforesaid parties collaborating with WHO. In this connection, you agree:

- (a) not to use the Information for any other purpose than discharging your obligations under the above-mentioned APW; and*
- (b) not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.*

However, you will not be bound by any obligations of confidentiality and non-use to the extent that you are clearly able to demonstrate that any part of the Information:

- (i) was known to you prior to any disclosure by or on behalf of WHO (including by the manufacturer(s)); or*
- (ii) was in the public domain at the time of disclosure by or on behalf of WHO (including the manufacturer(s)); or*
- (iii) becomes part of the public domain through no fault of your own; or*
- (iv) becomes available to you from a third party not in breach of any legal obligations of confidentiality.*

You also undertake not to communicate your deliberations and findings and/or those of the team(s) of experts in which you will participate, as well as any resulting recommendations to, and/or decisions of, WHO to any third party, except as explicitly agreed by WHO.

You will discharge your responsibilities under the above-mentioned APW exclusively in your capacity as an expert adviser to WHO. In this connection, you confirm that the information disclosed by you in the declaration of interest is correct and that no situation of real, potential or apparent Conflict of interest is known to you, including that you have no financial or other interest in, and/or other relationship with, a party, which:

- (i) may have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or*

- (ii) *may have a vested interest in the outcome of the evaluation of the product(s), in which you will participate (such as the manufacturers of those products or of competing products).*

You undertake to promptly advise WHO of any change in the above circumstances, including if an issue arises during the course of your work for WHO.

I hereby accept and agree with the conditions and provisions contained in this document.

Signed _____

Name (typewritten) _____

Organization _____

Place _____ Date _____

Appendix 4

Example of a standard operating procedure (SOP) for writing an SOP

1. Title

Standard procedure for writing a standard operating procedure (SOP)

	Signature	Date
Prepared by		9 May 2005
Authorized by		

2. Policy and objective

2.1 The procurement agency should have an SOP for each activity performed by the procurement agency. All SOPs should be in the required format and distributed with care to a predetermined list of personnel. SOPs should be authorized, implemented and kept up to date.

2.2 All SOPs should be written in English if any international use is expected, or in the local language if required only by local staff.

2.3 Documentation is a prime necessity in quality assurance. Its purpose is to define the system of control, to reduce the risk of error inherent in oral communication, to ensure that personnel are instructed in the details of, and follow the procedures concerned in a logical, reproducible manner.

2.4 There should be a written SOP for every critical or important activity in the procurement agency. SOPs should be written in the standardized format as attached.

2.5 A list should be kept of all SOPs required by the procurement agency.

2.6 Management should authorize SOPs prior to their distribution and implementation.

3. Responsibility

All members of staff should adhere to the SOP when drawing up the SOP. The project manager should supervise its implementation.

4. Action

4.1 Any person may initiate the first draft of an SOP. The headings (listed below) should conform to the attached format and should be used when writing the relevant sections of the SOP.

- 4.2 The SOP should include at least the following headings:
- A. Title
 - B. Policy and objective
 - C. Responsibility
 - D. Action
 - E. Addenda
 - F. Distribution
 - G. Review date
 - H. Revision history

The following information should appear under each heading.

A. **Title**

Write in clear language the title of the procedure to ensure understanding of the process that the SOP will be describing. The procedure should also contain a clear indication of who was responsible for the preparation, review and approval of the procedure.

B. **Policy and objective**

Describe the WHO or procurement agency policy regarding the matter to be dealt with under the SOP. Describe the objective to be reached in following the SOP.

C. **Responsibility**

Describe and list the people responsible for performing the activities listed in the SOP. Wherever possible, it is preferable to use job descriptions or position names for these people rather than names of individuals. Use of the personal names of staff members means the SOP has to be changed every time personnel changes occur.

D. **Action**

- 4.1 Describe the sequence of actions needed to perform the task.
- 4.2 List the actions in the order in which they need to be performed and number them from 1 to the end.
- 4.3 Explain all the steps in detail in clear, unambiguous, language.
- 4.4 Put the initials of the responsible person in brackets next to the action step if a specific person is responsible for the action step.
- 4.5 Read the completed SOP to determine whether it describes all the action steps to be followed from the start of the process to the end.
- 4.6 If a step leads to another SOP, then refer to the relevant SOP in that step.
- 4.7 If the SOP requires any records to be kept, draft the required format of the document to be completed and attach it to the SOP as an addendum.

- 4.8 Forward the SOP to the supervisor or person responsible for documentation and quality assurance.
- 4.9 Read the SOP and assess its suitability and applicability.
- 4.10 If any changes are to be made, make amendments to the SOP in ink and return it to the person who wrote the SOP for their comments.
- 4.11 Return the SOP to the supervisor.
- 4.12 Sign and date the SOP if satisfied with its contents.
- 4.13 Forward the SOP to the second person who is responsible for approving documentation.
- 4.14 The SOP should be signed and dated by the second person who is responsible for approving the documentation if he or she is in agreement with the contents.
- 4.15 Return the SOP to the person responsible for maintaining the documentation infrastructure.
- 4.16 If applicable, proceed with the steps for distribution and retrieval of the previous version of the SOP.
- 4.17 File the original SOP in the SOP file.

E. Addenda

- 4.18 Draft each addendum in such a manner that it leads the person responsible for completing the addendum to document all the required information.
- 4.19 Each addendum shall form part of the authorized SOP and shall be reviewed when the SOP is reviewed, or when necessary.

F. Distribution

- 4.20 Records shall be maintained of the distribution and retrieval of SOPs to ensure that superseded SOPs are not still in use anywhere.
- 4.21 Complete the table (see Addendum A, point 6) to indicate the name of the person to whom the SOP will be sent.
- 4.22 Make a copy of the original SOP and stamp it in red ink as “official copy”.
- 4.23 Only official copies of SOPs shall be controlled. SOPs not having a red stamp will be considered non-official and uncontrolled SOPs.
- 4.24 The person shall sign and date (in the appropriate space in the table (see Addendum A, point 6) on the original SOP), as proof of receipt of the SOP.
- 4.25 When the SOP is reviewed and amended, copies of the superseded SOP should be retrieved from all those who hold a copy when the new version is distributed.
- 4.26 When replacing the superseded SOP, the persons from whom it has been retrieved should sign (and date) the appropriate space on the distribution table in the original SOP.
- 4.27 Mark the original SOP as “superseded” on each page and file in the “superseded SOP” file.

4.28 Destroy all retrieved copies of superseded SOPs.

G. Review date

A date should be assigned on which the SOP will be reviewed to determine whether any changes are required to keep it up to date.

H. Revision history

4.29 To maintain a record of the history of the information on the SOP, complete the table regarding the history of the changes to the SOP (see Addendum A, point 7).

4.30 Each SOP should have a time limit for validity and should be reviewed before the end of the period of validity. This is an opportunity to consider whether the SOP still meets all its objectives and is appropriate for the work to be done and the methods of working. The updated SOP should go through the same writing and revision process.

5. Addenda

Addendum A contains an outline of the format of an SOP.

6. Distribution and retrieval

Name	Distribution		Retrieval	
	Signature	Date	Signature	Date

7. History

Date	Reason for change
	New SOP

Addendum A: Format of a standard operating procedure

WHO Logo Review date: 2006 Standard operating procedure	Document no.
--	--------------

1. Title

(indicate title)

	Signature	Date
Prepared by		9 May 2006
Authorized by		

2. Policy and objective

3. Responsibility

4. Action

4.1

4.2

4.3

5. Addenda

6. Distribution and retrieval

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

Date	Reason for change

Appendix 5

Example of an invitation for expression of interest

SIXTH INVITATION FOR EXPRESSION OF INTEREST (EOI)

In the context of dramatically increasing the access to, and affordability of, HIV/AIDS-related care and treatment, WHO, together with UNICEF, UNAIDS and UNFPA are inviting expressions of interest from manufacturers of pharmaceutical products in respect to the provision of drugs for the management of HIV-related diseases. The World Bank is in support of this effort.

This sixth invitation is published in order to increase the range of possible products and sources as a follow up to the interest that was expressed as a result of the first, second, third, fourth and fifth invitations published in 2000, 2001, 2002, 2003 and 2004.

Manufacturers should be committed to providing the above-mentioned products at preferential prices to developing countries. Interested manufacturers are encouraged to submit documentation and samples as specified below for various dosage forms and strengths of the products in the following categories:

I) **Antiretrovirals as single-ingredient formulations for use in adults and adolescents:**

- **Nucleoside/Nucleotide Reverse Transcriptase Inhibitors, including**
Abacavir
Didanosine
Lamivudine
Stavudine
Tenofovir
Zidovudine
- **Non-Nucleoside Reverse Transcriptase Inhibitors, including**
Efavirenz
Nevirapine
- **Protease Inhibitors, including**
Indinavir
Nelfinavir
Ritonavir
Saquinavir

Applications are also encouraged for single-ingredient formulations suitable for use in paediatric populations, that support existing international and or national treatment guidelines for paediatric antiretroviral therapy (ART).

As solid dosage formulations are the preferred formulations for treating children except for in the very young infant, manufacturers should also apply for reduced and/or scored solid dosage formulations of:

Zidovudine
Abacavir
Lamivudine
Nevirapine
Efavirenz

Also sought are syrups, solutions or dissolvable nucleoside/nucleotide and non-nucleoside formulations of the following products:

Zidovudine
Abacavir
Lamivudine
Nevirapine

For further information on paediatric formulations please consult: <http://www.who.int/3by5/paediatric/en/>

II) Antiretrovirals as fixed-dose combinations (FDC):

Applications are also encouraged for fixed-dose combinations of any firstline ARV regimens as described in the *WHO Guidelines for Scaling Up Antiretroviral Therapy in Resource Limited Settings – 2003 Revision*. For further information please consult: http://webitpreview.who.int/entity/3by5/publicatons/documents/arv_guidelines/en/

Fixed-dose combinations listed below:

For use in adults and adolescents:

- **Reverse Transcriptase Inhibitors**
 - Lamivudine + Stavudine
 - Lamivudine + Zidovudine
 - Lamivudine + Stavudine + Efavirenz
 - Lamivudine + Stavudine + Nevirapine
 - Lamivudine + Zidovudine + Efavirenz
 - Lamivudine + Zidovudine + Nevirapine
 - Lamivudine + Zidovudine + Abacavir
 - Tenofovir + Emtricitabine
- **Protease Inhibitors**
 - Lopinavir + Ritonavir

For paediatric use, reduced and/or scored solid dosage formulations of:

- **Reverse Transcriptase Inhibitors**
 - Lamivudine + Stavudine
 - Lamivudine + Zidovudine
 - Lamivudine + Stavudine + Nevirapine
 - Lamivudine + Zidovudine + Nevirapine
 - Lamivudine + Zidovudine + Abacavir

- **Protease Inhibitors**
Lopinavir + Ritonavir

Co-packaged preparations of the standard ARV combinations, for adult, adolescent and paediatric use are also sought. for further information on paediatric fixed-dose and/or co-packaged formulations please consult: <http://www.who.int/3by5/paediatric/en/>

- **Anti-infective drugs listed below:**
Antibacterial and antimycobacterial agents (other than MTB)

Azithromycin
Ceftriaxone
Cefixime
Ciprofloxacin
Clarithromycin
Clindamycin
Rifabutin
Spectinomycin

Antiprotozoal and Antifungal agents

Amphotericin B
Dapsone
Folinic acid
Fluconazole
Itraconazole
Pentamidine
Pyrimethamine
Sulfadiazine
Trimethoprim/Sulphamethoxazole

Antiviral agents

Acyclovir
Ganciclovir

- **Anti-cancer drugs**

Bleomycin
Etoposide
Vinblastine
Vincristine

- **Palliative care drugs**

Amitriptyline
Codeine
Chlorpheniramine
Ibuprofen
Loperamide
Morphine (oral formulation)

The medicines listed in this Invitation for Expression of Interest are those for which a need has been identified by the HIV/AIDS department, WHO. The submitted products should be of assured pharmaceutical quality and relevant data to support efficacy should be provided.

Procedure for submission of EOI

1. Submit a covering letter expressing the interest in participating in the project, confirming that the information submitted in the product dossiers is correct.
2. Submit a product dossier in the recommended format* as specified in the Guideline for submission of a product file which can be obtained by electronic mail from oakesl@who.int, also available on the the web page <http://mednet3.who.int/prequal>. The dossier should be accompanied by a sample of the product to enable analyses (e.g. 1 × 100 tablets).

*If the dossier is compiled in a different format (e.g. EU), then such a dossier can be submitted with a covering letter cross-referencing the pages where the relevant data can be found in accordance with the above-mentioned Guideline.

Submitted documentation reaching UNICEF Supply Division will be evaluated during March, May, July, September and November 2005. Documentation should be provided in English. Interested manufacturers should submit the above-mentioned information to:

UNICEF Supply Division

Reference: Accelerated Access to HIV/AIDS Care

SIXTH EOI

UNICEF Plads - Freeport

DK-2100 Copenhagen

Denmark

E-mail: supply@unicef.org

Tel: (45) 35 27 35 27 Fax: (45) 35 26 50 48

3. Submit a site master file for each manufacturing site as listed in the product dossier, in the recommended format, also available by electronic mail and on the web page <http://mednet3.who.int/prequal/> to

The Secretary

WHO/HTP/PSM/QSM

20 Ave Appia

1211 Geneva 27

Switzerland

Products and manufacturing sites assessed for acceptability and meeting the specified standards will be added to the list published on the project web page (<http://mednet3.who.int/prequal/>). Products and manufacturers included in this list may be invited to bid for the supply of products, individually or collectively, directly by member governments, by the aforesaid United Nations agencies and/or by associated NGOs.

The following criteria will be taken into account in the quality assessment process.

- Valid manufacturer's licence for production.
- Product registered or licensed in accordance with national requirements.
- Products manufactured in compliance with GMP as certified by the national regulatory authority and/or certified GMP inspectors.
- Product certificates exist in accordance with the WHO Certification scheme on the quality of pharmaceutical products moving in international commerce.
- Product dossiers of acceptable quality submitted and outcome of the assessment in respect of the prequalification procedure.
- Outcome of the inspection performed by or on behalf of the above mentioned agencies.
- Manufacturer demonstrates sound financial standing.

Only manufacturers THAT CAN SUPPLY APPROPRIATE PRODUCTS OF ACCEPTABLE QUALITY COMPLIANT WITH APPLICABLE REGULATORY REQUIREMENTS, WHO GUIDELINES AND LEGISLATION will be considered.

The United Nations procurement agencies reserve the right to determine specific conditions, as for example the exclusion of companies using child labour, or engaged in the manufacture of land mines or parts thereof.

Further references

For background information on drugs for the treatment of opportunistic infections in HIV/AIDS, please refer to www.aidsinfo.nih.gov/guidelines.

For background information on palliative care drugs, please refer to http://www.who.int/3by5/publications/documents/en/genericpalliative_care082004.pdf

Appendix 6

Pharmaceutical product questionnaire

I Product identification

Active pharmaceutical ingredient(s) (use INN if any):

Generic name of the product:

(Trade name requires prior approval by UNICEF)

Dosage form:

Tablets Capsules Ampoules Vials Other: _____

Strength per dosage unit: _____

Route of administration: _____

Oral IM IV SC Other: _____

Pack size (ml): 50 100 1000 Other: _____

Description of primary packaging materials: _____

Description of secondary packaging materials: _____

II Manufacturer of the product

Name, address and activities of the manufacturer(s) (or contract manufacturer(s)):

Name	Physical address	Telephone number, Facsimile number and e-mail contact details	Activity (e.g. packaging)

Are all sites listed above licensed by the relevant authority to perform the activity?

Yes No

Is the manufacturing site for THIS product prequalified by the procurement agency?

Yes No

Has the manufacturing method for each standard batch size been validated?

Yes No

List the standard batch size quantities: _____

III Supplier identification

(to be filled in if not identical to that indicated in question II)

Name: _____

Address: _____

Telephone number: _____

Facsimile number: _____

E-mail contact details: _____

Link with the product:

Marketing licence holder Distributor Manufacturer

Other: _____

IV Regulatory situation (licensing status) in the country of manufacture

Product registered and currently marketed: Licence number:

Product registered for marketing in the country of manufacture but not currently marketed: Licence number:

Product registered for export only: Licence number:

Product not registered (please clarify): _____

Please attach a Certificate of Pharmaceutical Product according to the WHO Certification scheme (WHO Technical Report Series, No. 863). Earlier version is not acceptable.

V Regulatory situation (licensing status) in other countries

List other countries where the product is registered and is currently marketed:

VI Finished product specifications

British Pharmacopoeia Edition (BP)

United States Pharmacopoeia Edition (USP)

International Pharmacopoeia Edition

Other: _____

Please attach a copy of the finished product specification, if different from BP, USP or International Pharmacopoeia specification.

Limits in % for the assay in active ingredient(s):

95–105%

90–110 %

Other: _____

Additional specifications to those in the pharmacopoeia (e.g. dissolution, syringeability): _____

Please attach a copy of the model certificate of analysis for batch release.

Are you willing to provide necessary information (analytical method) for the tests to be replicated by another control laboratory?

Yes

No

VII **Stability**

Stability testing data available:

Yes No

If yes, type and conditions of testing:

Accelerated testing 40 °C/ 75 % RH/ 6 months Other: _____

In the same packaging as specified under point I (page 1): Yes No

Real-time testing temperature:

ambient 25 °C 30 °C Other: _____

Relative humidity:

non-controlled 45% 65% Other: _____

Period of time:

1 year 2 years 3 years Other: _____

In the same packaging as specified under point I (page 1): Yes No

Can a stability report be forwarded within one week of being requested?

Yes No

Was the stability testing done on a product of the same formula, manufactured on the same site and packed in the same packaging material as the product that will be supplied?

Yes No

VIII **Label and insert information**

Shelf-life (years): 2 3 4 5 Other: _____

Storage conditions (e.g. "Do not store above 30 °C – Protect from light"):

Label language:

Bilingual English/French English French Other: _____

Package insert: Yes (attach a copy) No

IX **Samples**

Can free non-returnable samples be obtained upon request within one week of being requested? Yes No

X **Therapeutic equivalence**

Demonstrated:

by in vivo bioequivalence studies: Reference product: _____

Number of volunteers: _____ Country of study: _____

Year performed:

by another method claimed by the supplier/manufacturer (please describe briefly): _____

by in vitro dissolution tests: Reference product: _____

not demonstrated not relevant unknown

Can a copy of the report be obtained upon request within one week of being requested?

Yes No

Is the product used in the trial or test essentially the same as the one that will be supplied (same materials from the same suppliers, same formula, same manufacturing method)?

Yes No

XI **Active pharmaceutical ingredient(s) (APIs)**

(In case more than one active ingredient is used, please replicate this question.)

Do specifications and standard test methods exist for each API and excipient?

Yes No

Each API used (in INN if any):

has a Certificate of suitability to the European Pharmacopoeia (CEP)

Certificate no.: _____

The CEP is in our possession (including annex if any) _____

The CEP is in the possession of the finished product manufacturer (including annex if any) _____

has a drug master file (DMF)

registered in: (country) _____ registration no. _____

The full or open part of the DMF is in our possession _____

The full or open part of the DMF is in the possession of the finished product manufacturer

Quality standard:

BP USP EP International Pharmacopoeia

Other (e.g. "in-house"; specify): _____

No pharmacopoeia monograph exists*

*If there is no monograph in a recognized pharmacopoeia, then the following information should be provided and evaluated:

- chemical structure;
- if relevant, the isomeric nature of the active ingredient, including stereochemical

- configuration (e.g. racemate, pure (S)-isomer, 50/50 mixture of (Z)- and (E)-isomers;
- the solubility of the active ingredient in water at 25 or 35 °C;
- the solubility of the active ingredient in other solvents such as ether, ethanol, acetone and buffers of different pH (if the active ingredient is acidic or basic);
- other relevant physicochemical characteristics of the active ingredient such as partition coefficient (usually octanol/water) and the existence of polymorphs;
- copies of infrared, nuclear magnetic resonance (proton and C-13), ultraviolet and mass spectra;
- information on the chemical stability of the API, and on physicochemical stability if relevant (e.g. formation of a hydrate, change of polymorphic form).

Manufacturer (name, physical address + country): _____

GMP certified:

Yes (*attach a copy of the GMP certificate if any*) No Unknown

Certified by: _____

XII **Commitment**

I, the undersigned, _____

(*position in the company, e.g. General Manager, Authorized Person, Responsible Pharmacist*), acting as responsible for the company: _____

_____ (*name of the company*), certify that the information provided

(above) is correct and true.

(*If the product is marketed in the country of origin, tick the following boxes as applicable:*)

and I certify that the product offered is identical in all aspects of manufacturing and quality to that marketed in: _____

(country of origin), including formulation, method and site of manufacture, sources of active and excipient starting materials, quality control of the product and starting material, packaging, shelf-life and product information;

and I certify that the product offered is identical to that marketed in:

_____ (name of country), except:

(*e.g. formulation, method and site of manufacture, sources of active and excipient starting materials, quality control of the finished product and starting material, packaging, shelf-life, indications, product information*)

Date: _____ Signature: _____

Appendix 7

Example of a standard operating procedure for screening and assessing product information

1. **Title**

Assessing product files

	Signature	Date
Prepared by		9 May 2005
Authorized by		

2. **Policy and objective**

2.1 Each product file submitted by an interested manufacturer should be assessed as part of the prequalification process.

2.2 Each product file should go through a screening procedure.

2.3 Product files found to comply with the screening requirements will be retained for assessment.

2.4 The objective is to screen product files to determine whether these comply with the requirements. This will prevent loss of valuable assessment time, should the product files be incomplete when received.

2.5 The objective of the assessment process is to verify that the required information regarding safety, efficacy and quality of the product is documented and submitted in the required format. Where possible during inspections, and as a part of the verification process, the data and results should be verified to ensure that correct, accurate and reliable data have been submitted to the procurement agency.

3. **Responsibility**

Project Manager

Evaluators

4. **Action**

A. **Screening**

4.1 Unpack each product file onto the working surface in the presence of at least two other persons. Sign a sheet indicating the names of the persons responsible for opening the containers on that date.

4.2 Complete the relevant details in the “product received register”.

4.3 Record details such as the product number, date, product detail (INN), name of supplier, name of manufacturer(s), country of manufacturer(s), screening outcome, date manufacturer informed (Addendum A).

4.4 Allocate the product number in numerical order starting from 001.

- 4.5 The number should start with the year, e.g. 01 (for 2001).
- 4.6 Identify the project for which the product was submitted, e.g. HA for HIV/AIDS. The first product for the project would thus be numbered 01HA001.
- 4.7 Open a WHO file for the product. Write the product name, number and the name of the manufacturer on the outer page.
- 4.8 Write the product number on the product file and screening form for the product.
- 4.9 Screen the product file to assess its completeness. Confirm that all the required information, data and forms have been submitted by the manufacturer/supplier.
- 4.10 Use the attached screening form for this purpose (Addendum B).
- 4.11 Enter the relevant information in the appropriate column of the screening form as part of the screening process.
- 4.12 Once the screening is complete, make a copy of the screening form.
- 4.13 File the copy of the screening form in the screening form file.
- 4.14 Place the original of the completed screening form in the front of the product file.
- 4.15 If the product file is complete, place the product file in numerical order in the designated area marked "For evaluation".
- 4.16 If the product file is incomplete, place the file in the designated area, marked "Incomplete files".
- 4.17 Enter the outcome in the "product received register".
- 4.18 For each product file received, send a letter of acknowledgement of receipt to the manufacturer. For an "Incomplete file", inform the manufacturer in writing that the product file submitted was incomplete and cannot be considered for evaluation or assessment (see Addendum C for a model letter).

B. **Assessing product files**

Note: Each product file must be assessed by at least three evaluators.

Three evaluators should evaluate Part I (quality aspects) and at least two evaluators should evaluate Part II (bioavailability, safety and efficacy aspects).

Step 1 (Evaluator 1)

- 4.19 Take a product file from the section marked "For evaluation".
- 4.20 Use the attached product assessment report (Addendum D) for the purpose of evaluating the product information.
- 4.21 Go through each section and assess compliance with the required standards for the submission of the relevant information.
- 4.22 Record your findings in the report form.
- 4.23 On completion of the assessment record your name, signature and the date on the report form.
- 4.24 Record any specific problem associated with the evaluation of the product on a separate report form, entitled "Product-specific problem report" (Addendum E).
If you are evaluating Part 2, "Bioequivalence (safety and efficacy)", and the efficacy

part of the dossier is not included for all oral preparations, except aqueous solutions, at the time of administration, inform the manufacturer in writing that the product file was submitted without bioavailability aspects and cannot be evaluated at present.

4.25 Place the report forms in the front of the product file.

4.26 Replace the file in the section “For evaluation”.

Step 2 (Evaluator 2)

Perform steps equivalent to steps 4.19 to 4.26 above.

Step 3 (Evaluator 3)

Perform steps equivalent to steps 4.19 to 4.26 above.

Step 4

4.27 If a file contains the evaluation reports signed by three evaluators (quality aspects) and two evaluators (bioavailability), place the file in the area marked “Evaluation completed”.

4.28 Assess whether the relevant number of evaluators (three for quality aspects, and two for bioavailability) have evaluated each product adequately.

4.29 Collate the information in the reports. If additional information is required from the manufacturer or supplier, draft the letter on the basis of the information contained in the reports.

4.30 Request the additional information to be submitted within the specified period. Remind the manufacturer that failure to supply the requested information within the timescale requested may lead to exclusion of the product from further consideration.

4.31 Record the recommendation of evaluators on the list for the inspection of the manufacturing site.

5. Addenda

Addendum A: Product details

Addendum B: Screening form to assess the quality of the submission of EOI

Addendum C: Product information receipt

Addendum D: Product assessment report

Addendum E: Product-specific problem report

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

Name	Distribution		Retrieval	
	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be recorded in a table; see the model below.

Date	Reason for change

Addendum A: Product details

Product Number	Date	Product details (INN)	Name of supplier	Name of manufacturer(s)	Country of manufacture	Screening outcome	Date manufacturer informed	Inspection planned (Y/N)

Addendum B: Screening form to assess the quality of the submission of an expression of interest

Access to drugs and diagnostics of acceptable quality
 Pilot procurement quality and sourcing project

Complete the following:

Product submission number:

Product name	
Active pharmaceutical ingredient	
Strength	
Dosage form	
Pack size	
Name of supplier of drug products	
Address of supplier of drug products	
Name and address of manufacturer if different from that of the supplier above	
Name and address of manufacturer (and if appropriate of supplier) of the active pharmaceutical ingredient	
Date of submission	

(continued)

Country of origin of the submission	Supplier: _____ Manufacturer: _____		
Is the product licensed in	Japan USA EU*	YES YES YES	NO NO NO
If "Yes", proceed to Appendix 1 If "No", proceed to Appendix 2			

* (EU countries: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom).

Appendix 1

The following is included in the submission:

	YES	NO
A WHO-type certificate of a pharmaceutical product (CPP) issued by one of the regulatory authorities of ICH regions		
The summary of product characteristics (SmPC)		
Assessment report(s) issued by the respective regulatory authority		
WHO-type batch certificate from the manufacturer		
The packaging of the product is the same as that approved by the drug regulatory authorities of the ICH regions		1
The product information is the same as on the WHO-type CPP for at least:	_____	_____
Formulation		2
Strength		2
Specifications		2

¹ Stability testing data are submitted

--	--

² Arguments and/or data to support the applicability of the certificate(s) despite the differences are submitted.

--	--

If the answers to 1 and 2 are "no", then the EOI should be rejected.

Appendix 2

Check that the following has been submitted in the product documentation for EOI:

	YES	NO
Details of the product (Name of the product; approved generic name(s) (use INN, if any); visual description of the product; visual description of the packaging; strength per unit dosage and dosage form)		
Regulatory situation in other countries (Marketing authorization, withdrawn from the market, application rejected, deferred or withdrawn)		
API		
Properties Chemical structure; solubility in water, other solvents such as ether, ethanol, acetone and buffers of different pH; its isomeric nature including stereochemical configuration; partition coefficient and the existence of polymorphs; copies of infrared, nuclear magnetic resonance (proton and C-13), ultraviolet and mass spectra; information on the chemical and physico-chemical stability if relevant (e.g. formation of a hydrate, change of polymorphic form)		
Sites of manufacture Name and street address of each facility of manufacture (synthesis, production), including any alternative manufacturers GMP certificate attached (including for all alternative sites of manufacture being submitted)		
Route(s) of synthesis 1. Including reagents and reaction conditions; specifications for starting materials, reagents, solvents, catalysts and intermediates in the synthesis; synthetic by-products and degradation products 2. If a European certificate of suitability with any appendices is submitted, then an outline of the route of synthesis is sufficient 3. The manufacturer of the finished product should know the full details of the synthesis of the substance so that they are able to conduct a full set of tests on each batch. The results of such testing should be presented for at least two batches. The last option can be used only if the quality of API is described in a pharmacopoeia		
Specifications		
Pharmacopoeial requirements: copy of the monograph and tests, additional specifications, certificates of analysis, two batches, including results for impurities		
Non-pharmacopoeia: tests and limits, methods, results of validation		
Stability testing Results of stability, physical as well as chemical tests, methodology used (WHO guidelines or ICH guidelines), validation		
Finished product		
Formulation Formulation and administration unit, excipients not present in final formulation, the qualitative and quantitative composition, overages, function(s) of each excipient, ranges in the content of excipients justified and explained		
Sites of manufacture Name and street address of each facility. Indicate the activity, alternative manufacturers, major production step(s) – certificate issued, product information approved, summary basis of approval		

	YES	NO
Manufacturing procedure Outline of manufacturing and packaging Copy of the master formula and a copy of a manufacturing record Details of sterilization Stages of sampling and in-process control tests		
Specifications for excipients Pharmacopoeia: copy of the monograph, test methods referenced Additional specifications Non-pharmacopoeia: list of tests and for each excipient, including solvents, liquids to adjust pH, coatings, capsule shell, and inked imprint (on the dosage form), description of test methods, microbiological limits, colours EU/FDA/Japan		
Specifications for the finished product Two specifications: at release and end of shelf-life List general characteristics, specific standards: tests and limits for results for the finished product must be provided Analytical test procedures described (physicochemical properties, identity of API) Quantitative determination of active, deviations, purity tests, pharmaceutical tests, colouring antimicrobial or chemical preservatives, results of validation studies, comments on the choice of routine tests and standards provided Copy of pharmacopoeia monograph and verification data Results of batch analysis (inc. date of manufacture, place of manufacture, batch size and use of batch tested)		
Container/closure system(s) and other packaging Detailed description (inc. liner or wadding, details of composition); describe other (e.g. outer) packaging; state materials and specifications for part in contact with the product, or if protective. Parenteral: BP, EP, JP or USP		
Stability testing Results for each pack, methodology, validated (accuracy and precision recorded) Related compounds and decomposition: sensitivity, accelerated and real-time data, accelerated 40 °C and 75% RH for six months, real time 30 °C and 70% RH		
Container labelling Name, active ingredients, amount of each, batch number, expiry date, storage conditions, directions, warnings or precautions, name and address of the manufacturer, excipients known to be a safety concern		
Product information Copy approved by competent authority		
Patient information and package inserts Copies of package inserts and information for distribution		
Justification for any differences Arguments provided and/or data to support, validation data. Only minor differences are likely to be acceptable		
Interchangeability Multisource (generic): bioequivalence study. Bioequivalence of all oral preparations except aqueous solutions. Orally or parenterally administered aqueous solutions: chemical–pharmaceutical characteristics. Comparative clinical trial using clinical or pharmacodynamic end-points can be presented. End-points justified and validated for the compound and trial should be designed to show equivalence. Trial showing the absence of significant difference cannot be accepted Bioequivalence study report included		

	YES	NO
Report Study design, investigators, study site, study dates, preparations used, characterization of study subjects, study procedures, drug determination methods, measured drug concentrations, calculation methodology of pharmacokinetic parameters, statistical methodology and results of statistical calculations		
Summary of pharmacology, toxicology and efficacy of the product New active ingredients and new combinations of active ingredients: full safety and efficacy (EU, FDA, Japan)		

Accept

Reject

Hold

Reasons for rejecting or holding an application: _____

Addendum C: Product information receipt

Dear ...

Prequalification of manufacturers and suppliers of drug products

Thank you for submitting a product file after having indicated your company's interest in supplying drug products as part of the prequalification process of drug products to the United Nations organizations and interested procurement agencies.

We herewith acknowledge receipt of your product information sent to this office as part of the prequalification process.

The product information submitted has been screened to assess completeness of the submission in accordance with the guidelines that were sent to you after receiving your Expression of Interest (EOI) in participating in the prequalification programme. Kindly note that your submission is now pending the full assessment. It is possible that an inspection of the manufacturing site(s) will be performed in due course. Details of this will be advised to you once all the necessary arrangements have been completed.

OR

Kindly note that your submission was found to be incomplete. We therefore regret to inform you that no further evaluation will take place with regards to your product file, and that the manufacturer will be not be included in the prequalification process. Would you kindly contact this office within 30 days to enable us to make the necessary arrangements for the return of the information already submitted.

OR

Kindly note that your submission was found to be incomplete. It is missing the following information.

If you provide the missing data within X days, and it is of satisfactory quality, then your submission will go forward to full assessment.

Your cooperation is appreciated.

Addendum D: Product assessment report

Access to drugs and diagnostics of acceptable quality

Pilot procurement quality and sourcing project

Product number:		
Product name (API):		
Manufacturer:		
Product manufactured and registered/licensed in EU, Japan or USA	YES ¹	NO ²

This product evaluation report consists of two parts. Both parts should be completed as part of the assessment. The report should be written in clear unambiguous language referring to shortcomings or lack of data submitted, as communication with the manufacturer may result from the assessment.

Part One should be completed by at least three evaluators from different countries, responsible for assessing product quality including pharmaceutical and analytical aspects. (The report should be no longer than six pages.)

Part Two should be completed by an evaluator responsible for the assessment for bioavailability. (The report should be no longer than two pages.)

The report should be signed off by the person responsible for the evaluation and assessment of the product files.

Part I: Quality aspects

¹Product licensed/registered in the EU, Japan or the USA. Review the data submitted and comment (see also guidelines):

A WHO-type certificate of a pharmaceutical product (CPP) issued by one of the regulatory authority of ICH regions (EU, Japan, USA)
The summary of product characteristics (SmPC)
Assessment report(s) issued by the respective regulatory authority
WHO-type batch certificate from the manufacturer
The packaging of the product is the same as those approved by the drug regulatory authorities of the ICH regions
The product information is the same as on the WHO-type CPP for at least:

Formulation
Strength
Specifications

² Product not licensed/registered in the EU, Japan or the USA. Review the data submitted and comment:

Details of the product
Regulatory situation in other countries
Active pharmaceutical ingredient(s) (API) Properties of the API(s)
Sites of manufacture
Route(s) of synthesis
Specifications API described in a pharmacopoeia (specify the pharmacopoeia, its edition, and any supplement if relevant). The latest edition of the relevant pharmacopoeia should always be used. API not described in a pharmacopoeia
Stability testing
Finished product
Formulation
Sites of manufacture
Manufacturing procedure
Specifications for excipients

Specifications for the finished product
Container/closure system(s) and other packaging
Stability testing
Container labelling
Product information
Patient information and package inserts
Justification for any differences of the product in the country or countries issuing the submitted WHO-type certificate(s)

Evaluator (name):	Signature:	Date:
1		
2		
3		

Part II: Bioavailability (safety and efficacy)

(See also guidelines)

Bioequivalence study report
Summary of pharmacology, toxicology and efficacy

Evaluator (name):	Signature:	Date:
1		
2		
3		

Addendum E: Product-specific problem report

Access to drugs and diagnostics of acceptable quality
Pilot procurement quality and sourcing project

API:	
------	--

This product-specific problem report should highlight any specific problems identified during the evaluation of products. No mention should be made of the specific manufacturer's product. The objective is to identify any problems associated with a specific product containing a specific API, or specific to any dosage form.

Dosage form	
-------------	--

Problems

--

General recommendations

--

Appendix 8

Technical questionnaire for pharmaceutical manufacturers

1. General information on the manufacturer

Name, address, telephone, telefax, Internet address of the company:

Name	
Postal address	
Physical address	
Telephone	
Fax number	
Web site URL	
Contact e-mail address	

2. Affiliates

If the company is owned by another company, or belongs to a group of companies,

Please describe your position within the structure: _____

3. Regulatory issues

3.1 Good manufacturing practice (GMP)

Indicate the GMP standards (WHO, PIC/EU, FDA or other) with which the company complies: _____

Provide a copy of the latest inspection report or certificate whichever is appropriate.

3.2 Manufacturing licence for medicinal products

Please list the pharmaceutical dosage forms you are licensed to manufacture by the national regulatory authority and attach a copy of the manufacturing licence(s):

3.3 Inspection

Date of last inspection by a national or other competent drug regulatory authority:

Drug regulatory authority	Date

Please attach a copy of the last inspection report(s) or certificates for review on a confidential basis.

4. **Manufacturing**

4.1 **Manufacturing site**

Please state all the names and addresses at which manufacturing of pharmaceutical products to be prequalified takes place, and indicate in which year the factory was built. Include dates of upgrading and adaptation, as well as a description of the activity:

Name	Physical address	Year built and recent upgrades	Activity (e.g. all, compression, packaging, etc.)

4.2 **Personnel**

Please indicate the name, qualification and years of experience of the following key staff:

Position	Name	Qualification	Experience
Managing Director			
Technical Director			
Production Manager			
Quality Control Manager			
Quality Assurance Manager			

Number of personnel in total: _____

Number of personnel in production: _____

Number of personnel in quality assurance/control: _____

4.3 **Ventilation system**

Please indicate whether the manufacturing areas are equipped with controlled ventilation systems Yes No

If "Yes", please give a brief description of the ventilation system. (A diagram complementing the description can be submitted.)

If "No", explain reasons: _____

4.4 **Quality control**

Instrumentation?

Chemical laboratory in-house contracted out

Biological laboratory in-house contracted out

Microbiological laboratory in-house contracted out

4.5 **Contract manufacture**

Do you undertake contract manufacture for other companies? Yes No

If "Yes", please indicate the type of products (e.g. pesticides, antibiotics, hormones, cytotoxics, etc.) _____

Do you subcontract to other companies? Yes No

If "Yes", please list products and/or services that are subcontracted: _____

4.6 **Sterile products**

Do you manufacture sterile products? Yes No

Give a brief description of the method of sterilization used: _____

4.7 **Beta-lactam, highly sensitizing compounds, hormones, cytotoxic products**

Do you manufacture penicillins or other beta-lactam, highly sensitizing compounds, hormones or cytotoxic products? Yes No

If yes, does this production take place in a separate building provided with its own dedicated air-handling system? Yes No

4.8 **Complaints and recalls**

Do you have a recall procedure, which enables you to recall any product effectively and promptly within 24 hours from the distribution points or market? Yes No

Do you have a procedure for handling complaints? Yes No

Does it cover analysis of trends? Yes No

Please list significant product complaints and any recalls during the last three years:

Product	List complaints		
	Year 1	Year 2	Year 3

4.9 Research and development activities

Please indicate the type of activities and annual investment: _____

4.10 Production capacity

Product	No. of units per year	Last year's production units
Tablets		
Capsules		
Ampoules		
Vials, liquids		
Vials, dry powder		
Vials, lyophilized		
Ointments		
Liquids		
Powder for oral suspensions		
Suppositories		
Penicillin, tablets/capsules		
Penicillin, powder for oral suspension		
Penicillin, powder for injection		
Other, specify		

Are production capacity figures based on one or more shifts? (Tick appropriate box)

One

Two

Three

4.11 Stock

Do you maintain a permanent stock?

Yes No

4.12 Quality systems (including quality management and quality assurance)

Give a brief description of the quality management system, with specific reference to aspects such as procurement agency, documentation infrastructure, validation, training, statistical analysis, and other related aspects: _____

5. Products

5.1 Product licences

Please enclose a list of all products manufactured by your company for which you seek prequalification and which are authorized for sale. For each licensed product, please complete the table below and categorize as shown.

If possible, please attach an indicative price list.

Product	Marketed in the domestic market (Yes or No)	For export only (Yes or No)	Licences are held in the following countries	Name of contract manufacturer and country

5.2 Documentation

The following product documentation must be made available upon request for each product offered. Please indicate if this documentation is NOT available for any of the products on the list shown under point 5.1:

Product composition – master formula _____

Starting materials specification _____

Manufacturing and packaging specification _____

In-process test specifications and methods _____

Finished product specification _____

Packaging and labelling specifications _____

Analytical procedures _____

Upon request, “the common product questionnaire” must be completed and returned.

5.3 Samples

Are you willing to provide product samples and batch documentation (on a confidential basis) when requested? Yes No

5.4 Starting materials

List starting materials manufactured by the company or by affiliates, and indicate in the table below whether approved drug master files (DMF) or Certificates of suitability of the Monograph of the European Pharmacopoeia (CEP) are available.

Starting material	DMF (Mark ✓, and state number)	CEP (Mark ✓)

5.5 Stability studies and shelf-life

Do you perform initial and continuous stability studies on your products?

Yes No

Give a brief description of the stability procedure and programme. If “No”, explain reasons: _____

What type(s) of studies do you carry out?

Type (Mark with ✓)	Test conditions	
	Temperature (indicate)	Relative humidity (indicate)
Accelerated studies		
Real-time studies		

Explain if necessary: _____

How do you determine the shelf-life of your products? _____

5.6 Bioequivalence

Have you conducted in vivo bioequivalence studies for some of your products?
 Yes No

If “yes”, list the products studied and the reference products:

Product	Reference product	Country of study

5.7 Retention samples

Do you keep retention samples? Yes No

Samples:	Yes	No	Retention period	Storage conditions
Every finished product				
Active pharmaceutical ingredients				
Excipients				

6. Audit

Can we or any other representative designated by us perform a GMP audit of the manufacturing site? Yes No

Can (a) representative(s) from the national regulatory authority participate as observer(s) in the audit? Yes No

May we share the inspection report with the other procurement agencies “signatory” to this questionnaire? Yes No

Is a site master file (PIC or WHO format) available upon request? Yes No

Will any required additional information be provided if we wish to perform an audit of the company? Yes No

7. Other information

Contact person (commercial issues):

Name:	
Telephone no.:	
Fax:	
e-mail:	

Contact person (quality issues):

Name:	
Telephone no.:	
Fax:	
e-mail:	

Any additional information: _____

I hereby certify that the information given in this questionnaire and the attachments is correct.

Date

Signature

Name

Position in company

Appendix 9

Example of a standard operating procedure for planning of inspections

1. Title

Inspection, planning of site inspections

	Signature	Date
Prepared by		1 July 2006
Authorized by		

2. Policy and objective

2.1 Manufacturing sites should be inspected as part of the prequalification process. To enable the procurement agency to perform the inspections, they should be properly planned.

2.2 The objective is proper planning of site inspections to ensure that products will be sourced only from manufacturers that comply with international standards.

2.3 Proper planning of inspections should save time and resources (e.g. financial and human) through procurement agency planning.

3. Responsibility

Head of the Section or Department

Project Manager

Evaluator

4. Action

4.1 When assessing product information, make a list of all the products received (see Addendum A). Complete the table.

4.2 On the basis of the outcome of the assessment of the product information, decide which manufacturers should be inspected for prequalification.

4.3 Dossiers lacking information, or of unacceptably low quality, may lead to the manufacturing site failing to qualify for the inspection.

- 4.4 Group all the manufacturers in one country together to ensure that when a trip is undertaken to one country, more than one manufacturer can be included in the inspection trip where relevant.
- 4.5 Consult a map to see where the sites are located and plan the trip so as to prevent unnecessary loss of time through travelling.
- 4.6 Plot the sites on a table (calendar) and allocate at least 3 days for inspection of each manufacturing site, depending on the dosage forms manufactured and the size of the facilities.
- 4.7 Write a letter to the company informing them of the tentative date allocated for the site inspection. Request the company to indicate whether the dates are suitable to them, and also request them to submit a site master file.
- 4.8 Appoint inspectors for the inspection team. There should be at least two inspectors on the team, including the representative from WHO.
- 4.9 Send a letter to the national regulatory authority inviting an inspector from the inspectorate to participate in the inspection.
- 4.10 Inform the inspectors of the proposed dates for the inspection.
- 4.11 When the manufacturer confirms the dates for inspection confirm the date with the company and request the information listed in Addendum B.
- 4.12 Confirm the dates with the inspectors.
- 4.13 Send the inspectors copies of the SOPs needed to perform the inspections, as well as the terms of reference, confidentiality clause, no conflict of interest declaration and agreement for performance of work.
- 4.14 Make the relevant bookings (air travel, transport in the country where the inspection will be performed and hotel accommodation).

5. **Addenda**

Addendum A: Summary list of dossiers received

Addendum B: Manufacturer information

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be entered in a table; see the model below:

Date	Reason for change

Addendum A: Summary list of dossiers received

No	API	Strength	Dosage form	Supplier/Manufacturer	Manufacturing site	Country	Sample

Addendum B: Manufacturer information

1. General information

Name	
Physical address of head office	
Postal address	
Telephone number	
Fax number	
Contact person	
E-mail address	

2. Manufacturing licence

Please attach the manufacturing licence.

3. Product list

Please attach a list of products manufactured at this particular manufacturing site.

4. Inspections by the national regulatory authority

Date of last inspection by the national regulatory authority (NRA)					
List the NRA of other countries that have inspected the site, and dates of inspection	<table border="1"> <thead> <tr> <th>Country</th> <th>Date</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> </tr> </tbody> </table>	Country	Date		
Country	Date				

5. Manufacturing and testing

Physical address of manufacturing sites for the products indicated in the submission	
Telephone number	
Fax number	
Physical address of quality control laboratories (chemical and microbiological) used for testing the products in the submission	
Telephone number	
Fax number	
E-mail	

6. Recalls

Please list the products and reasons for implementing a product recall in the last 5 years.

Product and batch number (INN, strength and dosage form)	Reason	Date of recall

7. Complaints

If the company has had any product complaints in the last year, please complete the table below.

Products and batch number (INN, strength and dosage form)	Complaint and source	Corrective action taken

8. Site master file (SMF)

If the SMF for the manufacturing site was submitted previously:

Date submitted	
SMF number	

If the SMF has not yet been submitted to WHO, please attach it now. Please note that the SMF must conform to the requirements specified previously.

9. Audit/inspection

We herewith grant WHO permission to perform the inspection of the manufacturing site to assess compliance with good manufacturing practice, for the purpose of the prequalification of the manufacturing site and product. I declare that the information given above is true and correct.

Signature: _____ Date: _____

Name: _____

Position: _____

Appendix 10

Example of a standard operating procedure for preparing for an inspection

1. Title

Preparation for an inspection

	Signature	Date
Prepared by		11 May 2006
Authorized by		

2. Policy and objective

2.1 Each manufacturer should be inspected by the procurement agency to assess compliance with good manufacturing practices.

2.2 All inspectors should follow the SOP in preparing for the inspection(s).

2.3 The objective is to ensure that a standardized procedure is followed by all inspectors when preparing for the inspections to prevent inspections being performed by different inspectors in different ways. This should ensure consistency in performance between inspectors.

3. Responsibility

Project Manager

Inspectors

4. Action

All actions described here are taken from the details provided by the WHO publication *Quality assurance of pharmaceuticals*, Volume 2, Chapter 4: Inspection of pharmaceutical manufacturers and inspection of drug distribution channels. These guidelines or other similar systems operated by national drug regulatory agencies should be followed in detail.

4.1 Once the inspection has been allocated to the inspector, he or she should plan for the performance of the inspection according to the steps outlined below.

4.2 Verify the objective of the inspection that is to be carried out.

- 4.3 Clarify which type of inspection will be performed, e.g. routine GMP or follow-up inspection.
- 4.4 Decide whether the inspection will cover the entire factory or just part of it.
- 4.5 Determine what the scope and depth of the inspection will be to enable you to prepare for it properly. (For a company producing sterile products, prepare by reviewing the guidelines for sterile product manufacture in addition to the general GMP guidelines.)
- 4.6 Scrutinize the product information for the products in the prequalification procedure manufactured at this manufacturing site.
- 4.7 Decide how long it will take to carry out the inspection and plan the date when the inspection will take place.
- 4.8 Inform the manufacturer(s) in question of the proposed date for the inspection.
- 4.9 Ensure that the proposed date for the inspection is suitable for all members of the inspection team.
- 4.10 Decide on a chief or lead inspector to coordinate and lead the inspection.
- 4.11 The lead inspector will be the main spokesperson during the closing or exit meeting at the end of an inspection, and has the overall responsibility for the inspection report.
- 4.12 Inform other interested parties of the proposed or planned inspection, e.g. a regional office of the procurement agency or agency, or the national regulatory authority.
- 4.13 Review documentation relating to the manufacturer to be inspected such as a completed questionnaire.
- 4.14 In case of a follow-up inspection, and where the procurement agency or agency has a company file in which general correspondence and previous inspection reports are filed, review the correspondence.
- 4.15 If a site master file (SMF) exists and is available, study the SMF and make notes to be followed up during the inspection (e.g. available equipment, SOPs and records).
- 4.16 Study the layout and design of the manufacturing facility, and some of the systems the manufacturer has in place to ensure quality in manufacture of products.
- 4.17 Look at the information provided on the manufacturing licence and product licence. Make notes of the aspects that need to be inspected to confirm compliance with licence conditions, and to verify data during the inspection.

4.18 Review the reports of previous inspections, reports of adverse drug experiences and complaints, if any exist, as investigations and corrective action taken by the manufacturer should be verified during inspections.

4.19 For a special inspection, review records of the company in relation to complaints and recalls, and regulatory test results (surveillance) where available.

4.20 If an annual report is available, scrutinize the report and note the information in relation to financial aspects of the company, personnel issues and products manufactured.

4.21 If any complaints had been received about the manufacturer or products previously supplied, review the contents of the complaint, investigation, outcome and corrective action.

4.22 If self-inspection/internal audit reports were requested from the manufacturer, review the contents. (Such reports are normally not requested as some manufacturers consider that the inspectors should assess GMP compliance themselves, and not look at the company's own findings of inspections. Requesting such reports would be dependent on the policy of the procurement agency.)

4.23 Study the diagram of the facility to get a better understanding of the flow of material, personnel and processes in the facility.

4.24 If any manuals and/or procedures were submitted by the manufacturer, review these and prepare specific questions relating to the quality policy, validation policy and procedure for performing certain activities.

4.25 Draw up a checklist or aide-memoire of points to be verified during the inspection.

4.26 Draw up a programme for the inspection. Produce an outline of what will be covered each day and clarify what each member of the team will be doing every day or half-day of the visit. Indicate in the programme which sections or departments will be inspected, and when (for an example, see Addendum A).

4.27 Distribute the programme to the team members. In the case of an announced inspection, form the company of the proposed inspection programme.

5. **Addenda**

Addendum A: Example of an inspection plan

6. **Distribution and retrieval**

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

Name	Distribution		Retrieval	
	Signature	Date	Signature	Date

7. **History**

The history of changes to the SOP should be entered in a table; see the model below.

Date	Reason for change

Addendum A: Example of an inspection plan

Manufacturer	
Address	
Date	
Inspectors	

Day 1

Time	Activity
08:30	Arrival
08:45	Opening meeting and company presentation
09:15	Receiving area and stores
10:15	Sampling
11:00	Tea
11:15	Weighing
12:00	Packaging components
13:00	Lunch
14:00	Manufacturing (organize time depending on the dosage form(s))
17:00	Summary of the day's observations

Day 2

08:30	Manufacturing, continued
10:00	Tea
10:15	Quality control
12:00	Heating, ventilation and air-conditioning, water and other utilities
13:00	Lunch
14:00	Documentation
17:00	Summary
17:30	Closing meeting

Appendix 11

Example of a standard operating procedure for performing an inspection

1. **Title**

Performance of inspection

	Signature	Date
Prepared by		1 July 2006
Authorized by		

2. **Policy and objective**

2.1 Each manufacturer should be inspected by the procurement agency to assess compliance with good manufacturing practices.

2.2 All inspectors should follow the SOP for performing inspections.

2.3 The objective is to ensure that a standardized procedure is followed by all inspectors when performing inspections to prevent inspections being performed by different inspectors in different ways. This should ensure consistency in performance between inspectors.

2.4 One of the objectives is to control and enforce the general standards of production for products that may be sourced as a result of the prequalification procedure.

2.5 Through sequential examination of production and control activities of the manufacturer, the manufacturer of pharmaceutical products may be included on the prequalification list as a manufacturer of pharmaceutical products for possible supply of specified products to procurement agencies and other agencies.

2.6 During inspections, the performance of manufacture of products and data submitted in the relevant product information files should be verified.

3. **Responsibility**

Project Manager

Inspectors

4. Action

All actions described here are taken from the details provided in the WHO publication *Quality Assurance of Pharmaceuticals*, Volume 2, Chapter 4: Inspection of pharmaceutical manufacturers and inspection of drug distribution channels. These guidelines or other similar systems operated by national drug regulatory authorities should be followed in detail.

4.1 Clarification and definitions

4.1.1 Different types of inspections are identified in the WHO text referred to above. These include:

- routine inspection;
- concise inspection;
- follow-up inspection;
- special inspection; and
- quality systems review.

4.2 The performance of the inspection is dependent on the type of inspection; however, in principle, the basic aspects of this procedure can be followed for performance of an inspection.

4.3 A routine inspection is a full review of all aspects and components of GMP within a facility. It is appropriate to perform a routine inspection under the following circumstances:

- When there is a new expression of interest (EOI) from a manufacturer or a newly established manufacturer.
- When the listing on the prequalification list is due for renewal.
- If there have been significant changes such as new products or new product lines; modification to manufacturing methods or processes; or changes in key personnel, premises and/or equipment.
- If an inspection has not been carried out within the past 3–5 years.

4.4 A concise inspection is the evaluation of limited aspects relating to GMP compliance within a facility. (It is known as an abbreviated inspection in some countries.) A limited number of GMP requirements are selected by the inspector to serve as indicators of overall GMP compliance by the manufacturer. The inspector also has to identify and evaluate any significant changes that could have been introduced by the manufacturer since the last inspection.

4.4.1 Collectively, the selected indicators and the changes identified indicate the manufacturer's attitude towards GMP.

4.4.2 A concise inspection is appropriate under the following circumstances:

- Where a manufacturer has a consistent record of compliance with GMP through routine inspections in the past.
- Where a sample of aspects can be taken as a good indication of the overall level of compliance with GMP.

4.4.3 However, if the concise inspection uncovers evidence that the level of GMP compliance has fallen, a more comprehensive or full GMP inspection should be performed soon after the concise inspection.

4.5 A follow-up inspection is also referred to as a re-inspection or a reassessment of the manufacturer.

4.5.1 A follow-up inspection is performed specifically to monitor the result of corrective actions of the manufacturer following a previous inspection.

4.5.2 Depending on the nature of the defects and the work required, the follow-up inspection could be carried out between 6 weeks and 6 months after the original inspection took place.

4.5.3 The follow-up inspection is limited to specific GMP requirements that have not been observed or that have been inadequately implemented by the manufacturer.

4.6 There are a number of circumstances in which special visits or inspections may be necessary. A special inspection is undertaken to do spot checks. Spot checks could focus on one product, a group of related products, or specific operations e.g. mixing, or labelling. If there have been complaints about a specific product that suggest there may be defects, a special inspection could be performed to investigate the quality defects of the product. If there has been a product recall, this can also trigger an inspection, as would adverse drug reactions. In the above cases, the inspection would focus on the specific product or aspect of production that is suspect. A special inspection could also be performed to gather specific information, or to investigate specific operations of the manufacturer.

4.7 The purpose of a quality systems review is to review the manufacturer's quality system and to ascertain whether it has been shown to operate satisfactorily.

4.8 Plan the inspection to ensure that all areas for assessment are covered in the allocated timeframe. The length of time needed for an inspection is determined by a number of factors, including the type of inspection to be performed, the number of inspectors, the size of the company and the purpose of the inspection or visit.

4.9 An inspection can be performed over a period of a few days to several weeks.

4.10 The time taken will also depend on the size of the inspection team. One or more inspectors can perform the inspection as part of an inspection team.

4.11 If necessary, appoint a specialist to accompany the team during the inspection, e.g. for particular dosage forms, chemistry or another aspect, e.g. the manufacture of biologicals.

5. **Addenda**

Addendum A: Inspection programme

Addendum B: Documentation required for verification during the inspection

6. **Distribution and retrieval**

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. **History**

The history of changes to the SOP should be entered in a table; see the model below.

Date	Reason for change

Addendum A: Inspection programme

Manufacturer	
Address	
Date	
Inspectors	

Day 1

08:30 Arrival
 08:35 Opening meeting
 08:45 Company presentation
 09:00 Receiving area and stores
 10:30 Tea
 10:45 Sampling and weighing areas
 11:15 Packaging material stores and control
 12:30 Lunch
 13:15 Manufacturing areas
 15:30 Tea
 15:45 Manufacturing (cont.)
 16:30 Summary of findings, day 1

Day 2

08:30 Arrival
 08:35 Manufacturing area (cont.)
 10:30 Tea
 10:45 Laboratories
 12:30 Lunch
 13:15 Laboratories (cont.)
 15:30 Tea
 15:45 Utilities
 16:30 Summary of findings, day 2

Day 3

08:30 Arrival
 08:35 Utilities (cont.)
 10:30 Tea
 10:45 Documentation
 12:30 Lunch
 13:15 Documentation (cont.)
 15:30 Tea
 15:45 Preparation for closing meeting
 16:00 Closing meeting

Addendum B: Documentation required for verification during the inspection

1. Organigram
2. Job descriptions
3. Quality policy (e.g. quality manual)
4. Validation policy (e.g. validation master plan or programme)
5. Raw material specifications (for specific products)
6. Packaging material specifications
7. Manufacturing formula and method masters
8. Packing instructions master
9. Batch manufacturing records (verification against master documents)
10. SOP index
11. SOP: self inspection
12. SOP: recalls
13. SOP: complaints plus records
14. SOP: batch number allocation
15. SOP: planned preventive maintenance
16. SOP and record: planned preventive maintenance of specific equipment
17. SOP: training (plus record of personnel)
18. SOP: environmental monitoring plus records
19. SOP: water sampling and testing plus records
20. Validation protocol and report for specific products
- 21.
- 22.
- 23.
- 24.
- 25.
- 26.
- 27.
- 28.
- 29.
- 30.

Appendix 12

Example of a checklist for good manufacturing practices

It is recommended that inspectors prepare an aide-memoire to remind them of points to be checked during an inspection.

Aide-memoires can be prepared to cover one or more aspects, e.g.

- production
- quality control
- utilities
- lyophilization

The aide-memoire should contain key words to remind the inspector of aspects to be inspected.

An example of an aide-memoire is shown below.

Example: Aide-memoire for inspection of the lyophilization process:

Points to check	Notes
Dissolving Filtration Filling and stoppering Transfer Loading Freezing Vacuum Heating Stoppering Capping	
Validation: Design qualification (DQ) Installation qualification (IQ) Operational qualification (OQ) Commissioning Process qualification (PQ) Media fills Air samples Surface swabs Operator swabs Daily clothing Simulate process with media (not freeze) Smoke test (transport area) Transport Frequent fill volume Pre-cooling of shelves (no ice)	

Points to check	Notes
Freezing Cycle Rate – (slow = crystals, polymorphism) Manner Drying temp. < eutectic point Determine eutectic point, consistent Shelf loading variations <i>Validate:</i> shelf temperature product temperature condenser temperature pressure (chamber) pressure (condenser) time, temperature, pressure leakage in contamination (thermal fluid, oil) cleaning	
Cycle Eutectic point determination Scale up Vial size Batch size	
Sterilization of lyophilizer Moist heat used Each cycle Residue if applicable Biological Indicators Design: single door (double door, air class!)	

Appendix 13

Guidance on good manufacturing practices: inspection report

Guidance on Good Manufacturing Practices (GMP): inspection report. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series No. 908), Annex 6.

Available at:

http://www.who.int/medicines/areas/quality_safety/quality_assurance/inspections/en/

Appendix 14

Good storage practices

For a guide to good storage practices for pharmaceuticals, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series No. 908), Annex 9.

Available at:

http://www.who.int/medicines/areas/quality_safety/quality_assurance/distribution/en/

Appendix 15

Good trade and distribution practices

For a guide to good trade and distribution practices for pharmaceutical starting materials, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-eighth report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 917), Annex 2.

Available at:

http://www.who.int/medicines/strategy/quality_safety/tr917ann2.pdf

Appendix 16

Quality system recommendations for pharmaceutical inspectorates

For a guide to Quality systems requirements for national good manufacturing practice inspectorates, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 8.

Available at:

http://who.int/medicines/areas/quality_safety/quality_assurance/inspections/en/

This publication is intended to assist procurement agencies to procure safe, effective pharmaceuticals of suitable quality. The model described here focuses on four key agency activities: prequalification, purchase, storage and distribution of pharmaceutical products. The long-term goal of the recommendations made is the design and implementation of a uniform and harmonized system that will ensure procurement of pharmaceutical products of defined quality for supply to patients. The system should be based on a mutually recognized process of prequalification of products and manufacturers.

The publication is divided into six modules, with the first addressing the general requirements for the quality assurance system that should be in place at all procurement agencies. Module II sets out recommendations for agencies when they are evaluating their product needs, assessing the products offered, and the manufacturing and supply arrangements provided by the manufacturers. The next module describes principles of purchasing pharmaceutical products, and is followed by recommendations on how to receive and store them. Good distribution practices are covered in Module V, while the final module describes monitoring and reassessment of products and contracted-out activities. In addition to a useful glossary, the publication includes a number of appendices with sample forms and questionnaires to use when implementing the model, as well as the text of relevant WHO guidelines.

This is an interagency document published by the WHO Department of Medicines Policy and Standards on behalf of the organizations listed. The text was previously included as Annex 6 of the 40th Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series No. 937, Geneva, World Health Organization, 2006).



United Nations Population Fund



WORLD BANK