Annex 3

Model quality assurance system for procurement agencies

Background

The Expert Committee on Specifications for Pharmaceutical Preparations of the World Health Organization (WHO) adopted a Model quality assurance system for procurement agencies (MQAS) during a meeting in Geneva, Switzerland in 2005. This was subsequently published as Annex 6 in the Technical Report Series, No. 937 in 2006. Some procurement organizations have implemented the recommendations presented in the MQAS. Some donor organizations (including the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)) have endorsed the MQAS as part of their quality assurance policy for the procurement of pharmaceutical products with their funds. Several organizations have also prepared a tool to assess procurement agencies to establish the level of implementation and compliance with the MQAS.

Participants at a WHO/GFATM joint stakeholders meeting on Quality Assurance for Essential Medicines held in August 2011 in Geneva agreed that a working group consisting of representatives from the Committee for Medicinal Products for Human Use (CHMP), Crown Agents, Global Drug Facility (GDF), International Committee of the Red Cross (ICRC), International Development Association (IDA), Médecins Sans Frontières (MSF), Management Sciences for Health (MSH), Partnership for Supply Chain Management (PFSCM), Quality Medicines for All (QUAMED), International Union Against Tuberculosis and Lung Disease (The Union), United Nations Children's Fund (UNICEF), United Nations Office for Project Services (UNOPS), and the United States Agency for International Development (USAID), be created to develop a harmonized Assessment Tool that could be used by all with the aim of better use of resources by coordinating procurement agency assessments and working towards mutual recognition of procurement agency assessment findings, and to participate in the revision of the MQAS.

The Global Fund Secretariat contracted a consultant through a competitive process in 2012 to review the existing MQAS and to make recommendations to WHO (in case the need was identified to change or update the MQAS), to review tools used by procurement agencies in the light of the existing MQAS and to prepare a harmonized tool for the assessment of procurement agencies, based on the MQAS, through a consultative process.

Four informal meetings were also held at the Global Fund between 2012 and 2013 to discuss the MQAS, the comments, the draft tool, progress made and the way forward.

Since the first publication of the MQAS and its use by many organizations, it appeared that a revision would be timely and could include current developments.

A first proposal for revision of the MQAS was presented at the forty-seventh meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, in Amsterdam, Netherlands. The recommendations included in the report (WHO Technical Report Series, No. 981) of the forty-seventh meeting of the Expert Committee read as follows (excerpt):

> **8.1 Revision of model quality assurance system for procurement agencies**
>
> The model quality assurance system (MQAS) for procurement agencies was adopted by the Expert Committee in October 2005, since when it has been used by many organizations. … The revised MQAS and the proposed assessment tool were … circulated for comment in August 2012 by WHO following the usual Expert Committee consultation process. Comments were collated and the draft revised MQAS and the comments were presented to the Expert Committee for consideration.
>
> The Expert Committee considered the comments and proposed a number of amendments to the draft. The Expert Committee endorsed the proposal for a revision of the MQAS, and noted progress made to date.
>
> **8.2 Assessment tool based on the model quality assurance system**
>
> In August 2011, WHO and GFATM identified the need for a new assessment tool for procurement agencies in conjunction with the revision of the MQAS. The proposed assessment tool was based on the MQAS. A draft of the proposed tool was prepared during 2012 and was circulated for comment. The draft was being tested in a pilot process from August to December 2012, after which it would be further reviewed and revised according to the experience gained.

During 2012 the draft assessment tool was used in a pilot phase (July to December 2012) by different organizations procuring medicines. Comments received on the MQAS as well as additional comments based on the use of the draft assessment tool (to assess procurement agencies) were reviewed during a meeting of the working group arranged through the Global Fund, on 7 and 8 February 2013, at the Global Fund offices in Geneva.

The fourth informal consultation was held in June 2013 to discuss additional comments on the MQAS as well as the newly developed aide-memoire to be used in assessing procurement agencies. The objective of the revised MQAS and use of an aide-memoire is to promote and ensure that all procurement agencies follow the same standard. A model format for an inspection report was prepared. The product questionnaire was reviewed.

During its forty-eighth meeting, the WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted the updated MQAS together with the replacement texts for Appendix 6 Interagency finished pharmaceutical product questionnaire and Appendix 14 Guidance on good manufacturing practices: model inspection report. In addition, the aide-memoire was recommended for use and is published as Annex 4 in the report of the forty-eighth Expert Committee meeting (WHO Technical Report Series, No. 986).

Glossary

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

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.

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

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.

change control: A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

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.

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: The 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.

inspection: An official examination, normally conducted on site, of the compliance with WHO good manufacturing practices as referred to in this document. In some cases, an off-site review of documentation may be done in lieu of the on-site examination.

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 state 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 medicines 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: 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 *medicine* and *pharmaceutical product* (see below) are used interchangeably.

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

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

medicines legislation: The legal conditions under which pharmaceutical activities should be organized (see also *legislation* above).

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 *medicine*.

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 nutraceutical 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: A procurement agency in the context of this document is defined as any organization purchasing pharmaceutical products, vaccines, or other health products or otherwise involved in their *prequalification* (see above), purchasing, storage and distribution.

product information: 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 a part (the initial stage) of validation,

but the individual qualification steps alone do not constitute process validation. 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 medicines needs: A careful evaluation of the quantities needed of each medicine, based on either adjusted past consumption or anticipated pattern of diseases and standard treatment, which can be expected to match actual needs reasonably well.

stringent regulatory authority (SRA): A regulatory authority which is:

a. a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (as specified on www.ich.org); or
b. an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic and Health Canada (as may be updated from time to time); or
c. a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

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).

variation: Variation to an approved product questionnaire or product dossier that includes, for example, changes in formulation, specifications, or manufacturing process.

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 pharmaceuticals 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

I.1 Introduction

Procurement agencies often have to purchase and supply pharmaceutical and other health products using scarce resources. In many cases, product quality is compromised when products are obtained from unqualified sources. Procurement agencies may deal with various types of organizations, suppliers and customers, including medicines regulatory authorities, manufacturers, quality control laboratories, contract manufacturers, contract laboratories, traders, brokers, distributors and pharmacies. A quality assurance system should be in place to ensure that transactions with these partners ultimately result in procuring pharmaceutical products and other health products (hereafter referred to collectively as 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 procurement agencies and general principles may apply to the activities covered in subsequent modules.

I.2 Physical resources

I.2.1 Premises

I.2.1.1 Offices

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

I.2.1.2 Storage

The procurement agency should have sufficient space for storage and retention of products, 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 on product labels, 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.

I.2.2 Equipment

I.2.2.1 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, traceability of batches supplied to customers, and reports and inventory control. Hard copies (printouts) should be produced as required to provide documentary evidence of the activities.

I.2.2.2 Software

The software selected should be suitable for the intended use. The programs 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 programs used should be compatible so that data can be transferred between them without having to be re-entered. Where information is exchanged between the procurement agency and the manufacturer(s) by electronic means, appropriate programs 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 program 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.

Standard operating procedures (SOPs) should be implemented to ensure that back up of data is made at defined, regular intervals.

Back-up data should be stored in a secure place with access control, under suitable conditions (e.g. protected from fire hazard).

Systems should be in place to ensure that back-up data are accessible and will be readable in the future, when required.

I.2.2.3 Hardware

The hardware selected 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 plan should be in place to ensure that the system remains functional.

I.2.2.4 Telecommunications

There should be access to telephone and email systems to ensure instant communication.

I.2.2.5 Furniture

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

I.2.2.6 Office equipment

Office equipment should be provided and kept in working order.

I.2.2.7 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, including printer cartridges and printing paper, as well as any replacement parts not covered by a maintenance contract, should be provided.

I.2.3 Vehicles and transport

As the procurement agency is responsible for transportation and distribution of products, appropriate transport should be provided to ensure that the quality of the products is maintained. (For details see Module V.)

I.2.4 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.

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 effective systems in place to enable it to conduct all its financial transactions without delay.

I.2.5 Human resources

I.2.5.1 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 activities and volume 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 quality assurance, prequalification, purchasing, storage and distribution. The person responsible for quality assurance could also be responsible for prequalification. The personnel responsible for quality assurance/prequalification and the personnel responsible for purchasing should be independent of one another. One should not report to the other.

National legislation should be complied with, for example, requirements for a responsible person for purchasing, storage and distribution of pharmaceutical products.

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

I.2.5.2 Qualifications and experience

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

I.2.5.3 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.

I.2.5.4 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. Personnel 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 as strictly confidential and proprietary to the party collaborating with the procurement agency.

Confidentiality agreements should be considered where necessary. 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).

I.2.5.5 Conflict of interest

Before undertaking any work, key personnel in key activities (e.g. quality assurance, prequalification, purchasing, specification setting – 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;
- 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 their circumstances, for instance if an issue arises leading to a conflict of interest during the course of their work for the procurement agency.

I.2.5.6 Job descriptions

There should be written job descriptions, with definitions of responsibilities, for all key personnel. Personnel and their supervisor should sign and date the job description.

I.2.5.7 Organization chart

The procurement agency should have an authorized, current 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.

I.3 Documentation of policies and standards

Documentation is an essential 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 MQAS are described below.

I.3.1 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.

The quality manual should contain as a minimum:

(a) a quality policy statement, including at least the following:

  (i) a statement of the management's intentions with respect to the standard of service it will provide,
  (ii) a commitment to establishing, implementing and maintaining an effective quality management system,
  (iii) the management's commitment to good professional practice and quality of activities and services,
  (iv) the management's commitment to compliance with the content of these guidelines,
  (v) a requirement that all personnel concerned with the activities within the procurement agency familiarize themselves with the documentation concerning quality and the implementation of the policies and procedures in their work;

(b) the structure of the procurement agency (organization chart);
(c) the operational and functional activities so that the extent and the limits of the responsibilities are clearly defined;
(d) outline of the structure of documentation used in the procurement agency quality management system;
(e) the general internal quality management procedures;
(f) references to specific procedures, conflict of interest and code of conduct;
(g) information on the appropriate qualifications, experience and competencies that personnel are required to possess;
(h) information on initial and in-service training of staff;
(i) a policy for internal and external audit;
(j) a policy for implementing and verifying corrective and preventive actions;

(k) a policy for dealing with complaints;

(l) a policy for performing management reviews of the quality management system;

(m) a policy for the handling of out-of-specification (OOS) results;

(n) policy to select service providers and suppliers including reference to prequalification;

(o) a policy for storage and distribution of products.

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

I.3.2 Standard operating procedures

The procurement agency should have written, clear and detailed SOPs for all the activities to be performed in the procurement agency. Quality risk management (QRM) principles may be applied in determining the scope and extent of SOPs. 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.

SOPs should be reviewed periodically.

I.3.2.1 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.

I.3.2.2 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 (optional section, if not included elsewhere)

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

Responsibility

This section should list the person(s) and/or departments responsible for performing the activities listed in the procedure. It may be useful to refer to the position and/or department 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.

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.

I.3.2.3 Activities to be covered by standard operating procedures

There should be written SOPs that reflect the activities of the procurement agency and ensure consistency in the execution of the operation, task or activity.

The following list gives examples of activities which could be covered by SOPs. A more specific list is provided at the end of each Module of these guidelines:

- how to write an SOP (see Appendix 4),
- handling of complaints,
- document/record control,
- self-inspection,
- handling of recalls,
- monitoring of environmental conditions (e.g. temperature),
- monitoring supplier performance,
- identifying and reporting substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) products,
- evaluating offers received,
- ordering product(s) from supplier or manufacturer,
- retention of products,
- retention of product documentation,
- handling of product samples,
- stock management and inventory control,
- control, monitoring and recording of temperature and relative humidity,
- handling of materials and/or products requiring special storage conditions,
- budget management,
- financial analysis,
- traceability of batches supplied to customers,
- password control for personnel working with computers,
- how to make back-ups, and storage of data,
- ordering, storage and handling of consumables,
- managing signatories of bank accounts,
- management of the accounting system,
- performing financial audits,
- preparation and management of the code of conduct,
- establishment and maintenance of confidentiality agreements,
- preparation and maintenance of conflict of interest declarations,
- preparation of job descriptions,
- preparation of organization charts,

- preparation of the quality manual,
- distribution and retrieval of SOPs,
- change control,
- handling of variations,
- managing records and archives,
- establishing and maintaining contracts.

Each time the SOP is reviewed and amended, superseded versions of the SOPs should be removed from all user points listed and replaced with the updated version. The retrieval should be documented. The section and/or responsible person who receives the SOP should acknowledge the receipt thereof. Personnel should be trained appropriately in using the revised SOP.

I.3.3 Change control policy and handling of variations

I.3.3.1 Change control

The procurement agency should have a policy and procedure for change control. This policy should be designed to manage changes in the agency, e.g. changes to procedures, internal processes, or premises. The procedure should describe the process that will be followed to initiate the change, and the routing of the request for approvals to effect or reject the change. The review of the change request should include an assessment of the risk and impact of the change.

I.3.3.2 Variations

There should also be a procedure for handling variations to a prequalified product. Examples of variations include those that affect active pharmaceutical ingredients (APIs), formulation, manufacturing processes, analytical testing methods or packaging of prequalified products. The procedure should ensure that these variations are reported to the procurement agency before new batches are manufactured or before they are delivered and released for distribution.

Details of managing variations in product information are given in Module VI.

I.3.4 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 with 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
- provision of information and advice.

I.3.5 Guidelines on conflict of interest

The procurement agency should have a policy on conflict of interest which all personnel (including external experts, and consultants) should observe. An example of a guideline on conflict of interest is provided in Appendix 3.

The document should address at least the following points:

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

I.3.6 List of prequalified products, manufacturers and suppliers

The procurement agency should have a procedure for preparing and maintaining a list of prequalified products, manufacturers and suppliers, based on the outcome of the evaluation of product data and information and of 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 additions to and deletions from the list.

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

A current, authorized, access-controlled list of prequalified products and suppliers should be available. The list should be maintained by authorized personnel.

The list should contain at least the following information:

- name and physical address of manufacturer, including the approved site(s) of manufacture linked to each product;
- product details, including the brand name, International Nonproprietary Name (INN), dosage form, strength per dose and pack size;
- date of last (pre)qualification.

I.3.7 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 for a defined period of time. Access to these areas should be restricted to authorized personnel, as confidential information may be filed (including records of manufacture, testing and/or storage).

Records pertaining to batches of product procured should be retained for at least one year beyond the expiry date of the product or in accordance with customer requirements and national legislation, whichever is longer.

I.3.8 Contract arrangements

Where any activity is delegated to another organization (e.g. procurement agency, quality control laboratory, or distributor), this should be done by means of a written agreement between the two parties. The contract giver should ensure that the contract acceptor meets the requirements as recommended in these guidelines.

Module II

Prequalification

II.1 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 inspection.

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 inspection should ensure that the manufacturer is able to manufacture the product as specified in the product information questionnaire/dossier and in accordance with 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 MQAS. This should ensure that the manufacturers will be providing products as specified that meet all predetermined norms and standards. Full prequalification may not be required when products are already prequalified by the WHO Prequalification Programme, or registered by SRAs. It will assist procurement agencies in maximizing the use of resources and will avoid duplication of prequalification. Prequalification also reduces 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.2 Principles for prequalification

Prequalification procedures should be based on the following principles:

- reliance on the information supplied by the national medicines regulatory authorities (NMRAs);

- 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 good manufacturing practices (GMP);
- assessment of consistency in production and quality control through compliance with GMP as described in the latest update of the WHO publication *Quality assurance of pharmaceuticals* (*1*) and supplementary WHO GMP guidelines.

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.

Where prequalification is delegated to another party, this should be done by means of a written agreement between the two parties. The contract giver should ensure that the contract acceptor meets the requirements as recommended in this module.

II.2.1 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 is updated periodically (*2*). They will find this list a useful reference for establishing specifications for the medicines needed for their purposes.

II.2.2 Standards for prequalification

Current standards for prequalification can be found at: http://apps.who.int/prequal/default.htm

In principle, products should meet the recommendations made by WHO in *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products – a manual for medicines regulatory authorities* (*3*). Manufacturing sites should comply with WHO GMP.

II.2.3 Key persons and responsibilities

All key personnel responsible for prequalification should have appropriate training.

II.2.3.1 Staff responsible for prequalification

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

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

- establishing specifications for products;
- publication of invitations for expressions of interest (EOI) (if this mechanism is used). An example of an EOI is provided in Appendix 5;
- 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, for compliance with WHO GMP;
- the list of prequalified products and manufacturers.

II.2.3.2 Staff responsible for evaluation of product information

Where possible, the person responsible for the evaluation of the product information should be independent from the person evaluating the manufacturing site.

The key responsibilities of the unit or appointed individual 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 (for completeness on initial receipt);
- evaluation of product information (full evaluation to assess compliance with standards);
- informing manufacturers of the outcome of the evaluation of the product information;
- communicating with the person responsible for inspections of manufacturing sites.

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

II.2.3.3 Staff responsible for inspection of manufacturing sites

The key responsibilities of the unit or appointed 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;
- conducting inspections;
- preparation of inspection report;
- follow-up of CAPA after inspections;
- finalizing inspection reports;
- informing manufacturers of the outcome of the inspection.

As a minimum, the personnel/appointed person responsible for inspecting manufacturing sites should have relevant qualifications and experience in pharmaceutical manufacturing, quality assurance, GMP and good distribution practices (GDP), performing inspections and audits, chemistry and quality control. Ideally they should have an inspection background from working with a regulatory authority or experience in managing manufacturing sites.

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.2.4 Key steps in prequalification

The key steps in prequalification include soliciting and receiving product data and information, screening and assessment of the data and information, and assessment for compliance with standards for manufacture such as GMP.

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.2.4.1 Step 1: Soliciting information

Prepare product specifications for prequalification

Specifications for the product(s) to be prequalified should be prepared.

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 API(s)/INN;
- strength per dose;
- dosage form (route of administration).

Other aspects to consider include pack size, primary packaging materials and labelling requirements.

Once the specification is finalized, the information can be published widely to all manufacturers, or targeted to prequalified manufacturers according to the internal rules of the procurement agency. The information communicated should include at least:

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

Procedure for submitting product information

The procedure for submitting product information should be publicly available and accessible. In cases where this is not the case, reasons for the decision should be given and documented.

The procedure should be written in clear, unambiguous language and should contain information detailing 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 medicines regulatory agency, and instructions for cross-referencing an existing dossier with the prescribed submission format);
- 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 and a checklist for the product information may be added (optional).

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 three formats in which submissions should be made:

1. 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) (*4*) issued by a stringent regulatory authority, together with a summary of product characteristics (SmPC), or proof of the official registration of the product;
   – if the product is different to the one registered by the SRA, arguments and/or data to support the application should be submitted. This may include differences in formulation, strength or other specifications including packaging.

   Products registered for export purposes only, should be fully assessed unless these were approved or subject to a positive opinion under the Canada S.C. 2004, c. 23 (Bill C-9) procedure, or Article 58 of European Union Regulation (EC) No. 726/2004 or United States Food and Drug Administration (US FDA) tentative approval.
2. A standard product dossier as prepared for a national medicine regulatory authority should be submitted, provided it contains the appropriate information as required in the WHO guidelines, e.g. common technical document (CTD). 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. A completed questionnaire with information on the product should be submitted. An example of a pharmaceutical product questionnaire is shown in Appendix 6.

Process of submission

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

Manufacturers should be requested to state 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 within a specified time period, or if the information supplied is inadequate to complete the prequalification effectively.

II.2.4.2 Step 2: Receive product information

Receipt of 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 and marking of 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.

The procurement agency should have a clear policy regarding the acceptance of information after the specified closing date. Processing of late submissions should not normally be allowed. Only in exceptional instances should late information 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 information, and manufacturers should give reasons for late submission.

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

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

II.2.4.3 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
- 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.2.4.4 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 a reasonable period 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.

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.

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 reasonable period 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 – if deemed necessary based on risk assessment – in accordance with the finished product specification. Certificates of analysis of product samples should be made available to the procurement agency.

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* (*5*) seeks to establish a practical basis for the quality systems manual of a control laboratory which each country can adopt and adapt when preparing 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 (*6*). The use of a WHO-prequalified quality control laboratory or 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.2.4.5 Step 5: Plan, prepare and perform inspections

Each batch of every product procured by a procurement agency should be manufactured in compliance with WHO 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 APIs may be inspected, based on risk assessment, as part of the assessment procedure to ensure that the APIs were manufactured in accordance with WHO GMP.

Existing certificates

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

Similarly, a CPP is not a guarantee of compliance with GMP. Participation in the WHO Certification Scheme (*7*) is a voluntary process, and there is no formal assessment or evaluation of medicines 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 medicines regulatory authority has an established system which is known to comply with acceptable standards for evaluation and registration or 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. An example of requirements applicable to quality systems for the operation of inspection services can be found in Appendix 8.

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 production and quality control of pharmaceutical products. A sufficient number of inspectors should be appointed to carry out inspections within predetermined time frames.

Where possible, a representative from the procurement agency (the person responsible for prequalification with 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 curricula 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 9.

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 an SOP for planning an inspection is shown in Appendix 10.

As the manufacturer will be inspected as part of the process of prequalification for the supply of specific products to the procurement agency, inspectors should prepare for inspections by studying the product information submitted by the manufacturer.

Appendix 11 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 WHO GMP. An example of an SOP for performing an inspection is shown in Appendix 12.

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 an 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 MQAS. An example of a GMP checklist is shown in Appendix 13.

Waiving of inspections

The need for an inspection may be waived where there is evidence that the site was inspected and approved by an inspection authority which is a member of PIC/S; an ICH member or its associated country; or from the WHO Prequalification Programme for the manufacturing site under consideration, covering activities for the product(s) being prequalified, provided that:

- all aspects of GMP for the relevant product(s) have been covered;
- the approval was within the last 36 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.

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 WHO GMP. According to the findings, the recommendation following the inspection may for example be one of the following.

- The manufacturer is considered not to be operating at an acceptable level of compliance with WHO GMP and a follow-up inspection is recommended to verify implementation and acceptability of corrective actions.
- The manufacturer is considered not to be operating at an acceptable level of compliance with WHO GMP and a compliance report is needed to verify implementation and acceptability of corrective actions.
- 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 published in WHO *Guidance on good manufacturing practices (GMP): inspection report* (*8*) (see Appendix 14 for a model 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 noncompliance was observed, corrective actions and timelines for completing them should be suggested. A response with supporting 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.

II.2.4.6 Step 6: Finalize assessment process

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.

This 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 responsible 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. It should be product- and manufacturing-site-specific.

The list may be published in the public domain.

Information on prequalified sources should be transparent and made available to customers when required.

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. 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.2.5 Requalification and monitoring

Requalification should occur at regular intervals. Routine re-inspection of manufacturers should take place as required based on risk assessment but at least every five years. Routine reevaluation of product information or questionnaires should be done every five years. Non-routine reevaluation 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.

II.2.6 Monitoring of complaints

Complaints should be handled in accordance with a written procedure.

A written report of the complaint, investigation, effective implementation of corrective and preventive action (CAPA) and outcome should be available.

Any complaint concerning a pharmaceutical product or batch of products supplied should be thoroughly investigated and include a root cause analysis, risk assessment and effective CAPA to avoid recurrence. The nature of the complaint should be communicated to the manufacturer.

The outcome of the investigation should be communicated to the complainant.

II.2.7 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.

II.3 List of suggested SOPs

- communication between the procurement agency and national medicines regulatory authority
- assessment of product data and information for compliance with norms and standards
- assessment of manufacturing sites for compliance with WHO GMP
- assessment of product data and information submitted by manufacturers
- assessment report writing
- planning of inspection
- inspection report writing
- procedure for prequalification
- delegation of prequalification to another procurement agency
- establishing specifications for products
- publication of invitations for expressions of interest (EOI)
- preparation and maintenance of the guidelines for the compilation of product information
- preparation and maintenance of the list of prequalified products and manufacturers
- receipt of product information
- screening of product information (for completeness on initial receipt)

- informing manufacturers of the outcome of the evaluation of the product information
- communicating with the person responsible for inspections of manufacturing sites
- recruiting or appointing inspectors with appropriate qualifications and experience when necessary
- follow-up of CAPA after inspections
- training of inspectors when necessary
- informing manufacturers of the outcome of the inspection
- preparation of product specifications for prequalification
- publication of product specifications for prequalification
- receipt of information (including late arrivals) and record-keeping
- contracting of a quality control laboratory
- submission of samples to a contract laboratory
- investigating, handling and reporting out-of-specification results
- waiving of inspections
- decision-making process for acceptance or rejection of a manufacturer
- requalification
- handling of complaints
- cost recovery on a fee-for-services basis.

MODULE III

Purchasing

III.1 Introduction

Procurement should be done with the aim of purchasing effective, quality assured products, and should not be focused on price alone.

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 which carry out these key activities.

See also *Operational principles for good pharmaceutical procurement* as recommended by the Interagency Pharmaceutical Coordination Group (IPC) (*9*).

III.2 Procurement strategies

Strategic objectives for good pharmaceutical procurement include:

- selection of reliable suppliers of quality products;
- procurement of the most cost-effective pharmaceutical products in the right quantities and meeting the quality standards;
- mitigating possible risks;
- timely delivery;
- achievement of the lowest possible total cost (which includes but is not limited to the price, cost of analysis, and transportation).

Where the supplier is an entity other than the manufacturer, such a supplier should meet the standards recommended in this MQAS.

These objectives should be achieved through efficient and transparent management reflected in an appropriate 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 agency should ensure that the following principles are applied:

- prequalified products are purchased from approved manufacturers or suppliers;
- procurement and purchasing procedures are transparent;
- activities follow formal written procedures throughout the process, including explicit criteria for awarding contracts;
- independent contract review;
- purchasing is based on the defined procurement policy of the procurement agency;
- 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 and performance, delivery time, ethics, legal status, financial viability and minimum order quantities;
- intellectual property rights are respected in accordance with best practice and national law.

III.3 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, and selection of product(s) and manufacturer(s) preferably based on prequalification.

Whatever the procurement method, responses should be examined to ensure that offers have been received from invited suppliers and that the offers are substantially responsive to the defined terms and conditions. Awards should be made to the maker of the lowest acceptable offer for the prequalified product that meets the terms and conditions. The companies should be informed of the outcome.

A brief description of different procurement methods is given below. (See also *Operational principles for good pharmaceutical procurement* (IPC) (*9*); and *Managing drug supply* (MSH)) (*10*).

III.3.1 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" conducted by direct invitation to all prequalified suppliers. Procurement agencies should use restricted tenders to invite bids from prequalified suppliers for all health products and services whenever possible.

III.3.2 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 products and suppliers should be used.

III.3.3 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.3.4 Open tender

Open tender is the formal procedure by which all manufacturers, national and international, are invited to bid for the sale of 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 products, 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.4 Quality assurance in purchasing

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

III.5 Key activities in purchasing

III.5.1 Develop a list

The procurement agency should develop a list or catalogue of products, listed by INN, that are identified for purchasing based on need, the national list of essential medicines, and the WHO Model List of essential medicines (*2*).

The procurement agency should develop specifications for the products in accordance with what has been prequalified and the terms and conditions for procurement. These may include pack size, remaining shelf-life, and lead time, among others.

III.5.2 Quantification

All requests for products should include quantities. Accurate quantification of needs is essential to avoid shortages or excess stocks. Quantities purchased should be based on a reliable estimate of actual need.

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

III.5.3 Procurement method

The procurement agency should apply the procurement method according to their policy and procedures (see also section III.3 above).

III.6 Organization and responsibilities

Purchasing should be done by personnel with appropriate qualifications and training, following established procedures.

Each staff member who undertakes purchasing or provides support to purchasing should have a job description which clearly describes his or her tasks and responsibilities.

The personnel responsible for purchasing should be independent from those responsible for prequalification and quality assurance.

Key responsibilities may include:

- preparing requests for quotations or tender documents
- publishing and handling tenders (when applicable) according to best practices
- handling contracts
- price negotiations
- placing orders
- market research
- monitoring suppliers' performance.

The personnel 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.

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.

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

III.7 Monitoring of performance of prequalified manufacturers

There should be a procedure for continuous monitoring of the performance of the manufacturers and suppliers. This may be a joint responsibility of different sections/units and include quality assurance and purchasing, among others. If a decision is taken to remove a product, manufacturer or supplier from the list, the supplier or manufacturer should be notified and a mechanism should be in place to prevent purchasing from this supplier or manufacturer.

Monitoring may include:

- review of quality control results;
- verification that the product batches supplied have been manufactured in compliance with standards and specifications accepted in the product dossier through inspection;
- pharmacovigilance (e.g. management of adverse event reporting);
- monitoring of complaints;
- outcome of inspection of manufacturing sites;
- outcome of reassessment of product information;
- monitoring of direct and indirect product costs;
- monitoring of adherence to delivery schedules.

Random samples of batches of pharmaceutical product(s) supplied by prequalified manufacturers, taken in accordance with a predefined sampling procedure (based on risk assessment), should be sent for independent testing at a reliable quality control laboratory (e.g. a WHO-prequalified laboratory) for compliance with final product specifications as part of the continuous monitoring programme.

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.

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).

III.8 Country legislation

Customers requesting products from procurement agencies should be responsible for ensuring that the products supplied comply with the destination country's legislation on registration and licensing status and intellectual property rights.

III.9 Donations

Any procurement agency receiving donations should handle donated medicines in accordance with a written procedure to ensure that patients receive products of known, appropriate quality. The WHO *Guidelines for drug donations* (*11*) outline the key issues. The principles established in these guidelines should be followed.

III.10 List of suggested SOPs

- selection of suppliers and products
- quantification of products
- calculation of the lowest possible total cost
- ensuring that prequalified products are purchased from approved manufacturers
- awarding contracts
- independent contract review
- purchasing of products
- considering intellectual property rights
- preparation of requests for quotations or tender documents
- publishing and handling tenders
- handling contracts
- price negotiations
- market research
- monitoring suppliers' performance
- pharmacovigilance
- monitoring of direct and indirect product costs
- monitoring of adherence to delivery schedules
- donations.

MODULE IV

Receipt and storage of purchased products

IV.1 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.

It is recommended that premises are designed in such a manner that products will follow a unidirectional flow from receiving to dispatch, to avoid any possible mix ups.

Effective measures should be in place to ensure the security of materials and products.

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 laboratory, 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 laboratory must be capable of undertaking the full range of tests required. Any subcontracting of such work to third parties should be managed correctly and the responsibility for the quality of the work done should be clearly defined.

The principles established in the WHO guide to good storage practices for pharmaceuticals (*12*) (see Appendix 15) should be followed throughout the steps described in this module.

IV.2 Pre-shipment quality control

Note: Pre-shipment is considered at manufacturer level prior to sending the product(s) to the procurement agency or customer.

Each batch of finished product should be tested by the manufacturer to determine that it conforms satisfactorily to its finished product specification, prior to supply.

The procurement agency may decide, using a risk-based approach, to test selected batches.

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

IV.3 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.

Products should be quarantined until test results confirm that the products meet all of the requirements, specifications, terms and conditions of the purchase order. It is strongly recommended that a review of certificates of analysis 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, the supplier's labels and transport conditions (e.g. temperature and relative humidity as appropriate). 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.

Containers and products should be visually inspected for possible contamination, tampering and damage, expiry date, compliance with labelling and packaging instructions, 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.

V.4 Post-procurement quality control

Note: Post-procurement is considered at procurement agency level or at the level of the customer.

IV.4.1 Sampling

The procedures for receipt of supplies should include random sampling for independent laboratory analysis by the procurement agency to ensure that pharmaceutical products meet the required standards. Sampling should be performed in accordance with a written procedure and with national legislation. 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 plans and sampling instructions that are based on risk assessment. (See also WHO guidelines on sampling and International Organization for Standardization (ISO)/American National Standards Institute (ANSI) guidelines on sampling (*13–15*).) 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 written release or rejection is obtained.

IV.4.2 Rejected materials

Stringent precautions should be taken to ensure that rejected materials and pharmaceutical products cannot be used. This can be achieved through separate storage or by means of a validated computerized system. Rejected materials may 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.5 Storage of materials and products

IV.5.1 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.5.2 Storage areas

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products, including space for segregation of rejected, expired, recalled or returned stock. This includes appropriate measures for narcotics and psychotropic medicines which should be kept locked up and controlled under specific procedures as required by national legislation.

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

Precautions should be taken to prevent unauthorized entry into the storage areas. A security system sufficient to safeguard all areas of the warehouse and offices should be in place.

A written procedure for fire control measures should be in place, including prevention of fire, fire detection and fire drills. Fire detection and fire-fighting equipment should be serviced regularly.

Smoking and eating should not be permitted in the storage areas.

Toilet and washing facilities should be sufficiently separated from storage areas.

IV.5.3 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-expiry, first-out (FEFO) 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 and contents on pallets should be stacked in a manner that ensures that there is no damage to containers on the lower level.

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 WHO GSP (http://www.who.int/medicines/areas/quality_safety/quality_assurance/GuideGoodStoragePracticesTRS908Annex9.pdf).

Cold rooms should be provided for storage of materials and products requiring storage under specified conditions between 2 and 8 °C. Cold rooms should be qualified, which includes temperature mapping. The temperature should be controlled, monitored and recorded with results reviewed for compliance with the specified limits. Where electronic systems are used for data collection, provision should be made for back-up of data at regular and defined intervals. Cold rooms should be fitted with alarm systems that will alert personnel of out of limit conditions.

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 an appropriate monitoring device.

IV.5.3.1 Monitoring of storage conditions

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.

The equipment used for continuous monitoring should be calibrated at suitable predetermined intervals and the results should be recorded, reviewed and retained. Out of limit and out of trend results should be investigated in accordance with an SOP and appropriate action should be taken. 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.

IV.5.4 Repackaging and relabelling

Where repackaging or relabelling is done, compliance with the requirements of national legislation and WHO GMP will be considered mandatory.

IV.5.5 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, materials, or 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.5.6 Stock control

Stock rotation and control is best maintained by the use of a validated 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.

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. Records should be maintained.

Damaged containers should not be issued unless it is certain that the quality of the material inside is unaffected. Any damaged containers should be reported without delay to the person responsible for quality assurance. Any action taken should be in accordance with an SOP and documented.

IV.5.6.1 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.

IV.5.6.2 Recalled materials and products

Recalled products should be identified, recorded, reconciled, 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 in coordination with the manufacturer. An assessment should be made by an appropriately qualified and experienced member of staff.

IV.5.6.3 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 customer should be destroyed in compliance with national requirements 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. Any action taken should be recorded.

IV.5.6.4 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 in accordance with national regulations.

IV.5.7 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/expiry dates. 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.

IV.6 List of suggested SOPs

- receipt of products
- storage of products
- access control to areas
- handling of damaged containers
- preshipment sampling and testing
- postshipment sampling and testing
- handling of rejected products
- handling of returned products
- procedure for gowning
- fire control
- environmental monitoring
- cleaning of storage areas
- FEFO
- rodent and pest control
- packaging of freeze-sensitive materials
- temperature mapping studies
- handling of toxic and flammable goods
- handling of spillages
- stock reconciliation
- control of obsolete materials and products
- handling of waste materials.

MODULE V

Distribution

V.1 Introduction

A well-managed distribution system should achieve the following objectives:

- maintain a constant supply of medicines;
- keep medicines in good condition throughout the distribution process;
- ensure controlled transport conditions;
- minimize losses of medicines due to spoilage and expiry;
- maintain accurate inventory records;
- rationalize medicine storage points;
- use available transportation resources as efficiently as possible;
- reduce theft and fraud;
- provide information for forecasting medicine 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 practices for pharmaceutical starting materials* (*16*) (see Appendix 16) should be followed.

V.2 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.

Where temperature excursions occur during transport, risk assessment should be done to ensure that an informed decision is taken as to the fate of the products.

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

V.3 Cold chain

Special care should be exercised when using a cold chain. If goods are distributed under controlled cool or cold conditions, appropriate containers should be used. Containers should be packed following established standard procedures to ensure that products are not negatively affected.

When a cooling agent, such as dry ice, is used in cold chains, it is necessary to ensure that the material or product does not come in contact with the cooling agent as this may adversely affect the quality of the product, e.g. as a result of freezing.

The process should be validated to cover the expected transport time, taking into account expected environmental conditions.

V.4 Temperature monitoring and records

Calibrated devices should be used to monitor conditions such as temperature during transportation. Records should be available for review.

V.5 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.6 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 sea or by air.

All legislation that may affect these requirements must be complied with.

V.7 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.8 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;
- transport and storage conditions.

V.9 Traceability

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

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.9.1 Recalled materials and products

When required, materials and products should be recalled following a written procedure. Written records of all major actions signed by the person responsible for carrying out each action should be maintained.

Recalled products should be identified, recorded, and reconciled.

The effectiveness of the arrangements for recalls should be evaluated at regular intervals.

V.10 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.11 List of suggested SOPs

- packaging of products in containers
- maintaining appropriate storage conditions during transport
- maintaining the cold chain
- calibration of temperature sensors and devices
- verification of authorized recipients
- labelling of outer containers
- maintaining dispatch records.

MODULE VI

Reassessment

VI.1 Introduction

The quality of all products and services procured in accordance with this MQAS 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.

II.2.5 Requalification and monitoring

Requalification should occur at regular intervals. Routine reinspection of manufacturers should take place as required based on risk assessment but at least every five years. Routine reevaluation of product information or questionnaires should be done every five years. Non-routine reevaluation 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, taken in accordance with a predefined sampling procedure (based on risk assessment), should be sent for independent testing at a reliable quality control laboratory (e.g. a WHO-prequalified laboratory) for compliance with final product specifications as part of the continuous monitoring programme.

VI.2 Reevaluation of manufacturers

Reinspection of manufacturers should take place at regular intervals based on risk assessment, but no less often than every five years.

Procurement agencies should have a mechanism in place that ensures that manufacturers inform them immediately of any changes to the manufacturing site, manufacturing process 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 reinspection; 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 noncompliance with the requirements for prequalification.

VI.3 Reevaluation of products

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

Procurement agencies should have a mechanism in place that ensures that manufacturers inform them of any contemplated changes to the product that may affect its safety, efficacy or quality. With regard to the product, manufacturers should, for instance, report the following:

- change of manufacturing process, site or equipment relating to the product;
- change of contract manufacturers;
- change of pharmaceutical product release control laboratories;
- change of 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;
- change of specifications;
- change in shelf-life.

Based on the information submitted, the person responsible for prequalification should decide whether to approve the changes or whether to request additional data.

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 reevaluation 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 as not being in compliance with the agreed specifications of the product or as revealing failure(s) regarding safety, performance or quality of the product;
- 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 publication *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for medicines regulatory authorities* (*3*) gives guidance on when to proceed with which type of reevaluation;
- 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.4 Monitoring of contracted services

Monitoring of the performance of contractors (e.g. prequalification, quality control, storage, transport and distribution) and follow-up of noncompliance should be carried out according to a written procedure. It should include continuous monitoring, as well as periodic review and renewal of the contract.

The procurement agency should document any reported problems with service and inform the contractor of each problem. Continuous monitoring should also cover 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.

Contracted laboratories should comply with the principles of GLP (*17*). The accreditation status alone does not guarantee compliance with GLP. The performance of contracted laboratories should be continuously monitored.

VI.5 List of suggested SOPs

- reassessment of product data and information
- reinspection of suppliers and manufacturers
- handling variations
- monitoring of the performance of contractors
- review of agreements.

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Further reading

Guidelines for good clinical practice for trials on pharmaceutical products. In: *WHO Expert Committee on the use of Essential Drugs, sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 8 (http://www.googlesyndicatedsearch.com/u/who?q=Good+clinical+practice+for+trials+on+pharmaceutical+products&sa=Go&sitesearch=who.int&domains=who.int

Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant (http://apps.who.int/medicinedocs/en/d/Js2273e/13.6.html#Js2273e.13.6).

WHO guidelines on quality risk management. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-seventh report*. Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2 (http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/index.html).

WHO Model Formulary (http://www.who.int/selection_medicines/list/en/).

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 nonperformance 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;
- 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.

Staffs 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;
- 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 signifi cant 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 Organisation Mondiale de la Santé

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 be half 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

	Distribution		Retrieval	
Name	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 first-line 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
  Ibuprophen
  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).

   Submitted documentation reaching UNICEF Supply Division will be evaluated during March, May, July, September and November 2005. Documentation should be provided in English.

* 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

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
Email: 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/genericpalliativecare082004.pdf

Appendix 6

Interagency finished pharmaceutical product questionnaire based on the model quality assurance system for procurement agencies

Please fill out one separate form for each pharmaceutical product

Section 1: Administrative section

1.1 **Product identification**

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

_____

1.1.2 Generic name of the product:

_____

1.1.3 Trade (proprietary) name (if any):

_____

1.1.4 Dosage form:

☐ Tablets ☐ Capsules ☐ Injectable ☐ Syrups/oral liquids

☐ Other: (Please specify)

_____

1.1.5 Strength per dosage unit: _____

1.1.6 Route of administration:

☐ Oral ☐ I.M. ☐ I.V. ☐ S.C.

☐ Other (Please specify)

_____

1.1.7 Please provide the formulation of the product (complete qualitative and quantitative composition including active ingredient(s), overages if any and excipients). Please also indicate the standard for each ingredient (e.g. BP, USP, in-house). Mention specifically if the product is a fixed-dose combination (FDC) or co-packaged: Annex A

_____

_____

_____

1.1.8 Please state inactive ingredients (excipients) of medical/pharmaceutical relevance, amount in dosage form or per dosage unit (e.g. contains alcohol 10%, paraben…….)

1.2 Packaging

1.2.1 Description and materials used for primary packaging[1] and pack size (quantity of dosage-form units per pack): Annex B

1.2.2 Description, pack size and material used for secondary packaging materials: Annex C

Contact details

1.3 Manufacturer identification

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

Name of manufacturer, contract manufacturer if any	Reference of manufacturing licence, date and expiry date, if any	Physical address. Please specify units, and block if existing	Telephone number, facsimile number and email contact details	Activity (e.g. packaging)

1.4 Supplier identification

(to be filled in if not identical to that indicated in 1.3)

Name of company: _____

Physical address (complete details required): _____

_____

Telephone number: _____

Fax: _____

Website: _____

Email: _____

[1] For example, HDPE bottle, Alu-Alu strip, neutral glass vial.

Link with the product

☐ Marketing licence holder ☐ Manufacturer
☐ Distributor/wholesaler ☐ Other

1.5 Note for the applicant

Please note that the information in this questionnaire can be shared confidentially among ICRC, MSF, WHO procurement centre, UNFPA and UNICEF for procurement purposes. If you have any objection, please indicate this to the relevant agency that you are dealing with.

Has the dossier been submitted to any of the following agencies: ERP, ICRC, MSF, WHO procurement centre, UNFPA, UNICEF?

Please provide the date of the submission: _____

1.6 Regulatory (licencing) status

1.6.1 In the country of manufacture

☐ Product registered and currently marketed

Licence no.: _____

Provide a copy in Annex D

☐ Product registered for marketing in the country of manufacturing but not currently marketed

Licence no.: _____

☐ Product registered for export only

Licence no.: _____

☐ Product not registered *(please clarify)*: _____

- Please attach a certificate of pharmaceutical product (CPP) according to the WHO Certification Scheme (WHO Technical Report Series, No. 863) in Annex E. An earlier version is not acceptable).
- If a CPP cannot be obtained from the national medicines regulatory authority (NMRA), please state the reason and send an equivalent document if any.
- Submit recent as well as historical deficiency letters issued by the WHO Prequalification Programme (PQP)/SRA in relation to the specific product dossier in Annex F.

1.6.2 In other countries

List other countries where the product is registered and is currently marketed *(please provide registration number)*

_____

_____

1.6.3 WHO prequalification status, if applicable

This product is prequalified by WHO/PQP.[2]

☐ Yes ☐ No

If yes, please attach a copy of the relevant WHO/PQP acceptance letter signed by your company (Annex G).

1.6.4 Submitted for prequalification: indicate date of submission, WHO acceptance letter for product dossier review mentioning the WHO reference number assigned by WHO for this specific product (Annex H)

_____

1.7 Samples for technical evaluation

1.7.1 Samples of finished product and insert information

You are required to please provide a sample of the finished product(s) offered, and relevant inserts/leaflets. (If you cannot submit any of the above with the questionnaire, please state why not and when you will do so.) (Annex I)

1.7.2 Label language (attach a copy): primary packaging

☐ Bilingual English/French ☐ English ☐ French

☐ Other (specify) _____

1.7.3 Label language (attach a copy): secondary packaging

☐ Bilingual English/French ☐ English ☐ French

☐ Other (specify) _____

For oral powder for suspension and powder for injection, in-use periods and storage conditions after reconstitution should be stated on the product label.

1.7.4 Patient information leaflet (Annex J)

☐ Yes (attach a copy) ☐ No

[2] WHO Prequalification website: http://apps.who.int/prequal/.

Section 2: Active pharmaceutical ingredients

(If there is more than one active ingredient or more than one manufacturer is used, please replicate this section.)

2.1 Details of API used (INN if any):

_____

_____

2.1.1 Manufacturer

Manufacturer (name, physical address and country)/manufacturing site (please list all alternative sources):

_____

_____

GMP certificate from the country of origin: attach a copy of the GMP certificate, if available, in Annex K.

Last inspection of API manufacturing sites performed, when available, (please attach GMP certificate or relevant letter) by:

- ☐ Finished product manufacturer
- ☐ WHO Prequalification Programme, Geneva
- ☐ EDQM
- ☐ US FDA
- ☐ PIC/S members
- ☐ Others (specify)
- ☐ None of above

Outcomes and date:

_____

_____

Is/are the API(s) used to manufacture this product WHO-prequalified?

☐ Yes ☐ No

2.1.2 API specifications

- ➢ API specifications:
  - ☐ British Pharmacopoeia (BP) (edition/year):
  - ☐ United States Pharmacopeia (USP) (edition/year):

☐ *The International Pharmacopoeia* (Ph.Int.) (edition/year)

☐ Others (specify): _____

☐ Specifications additional to those in the pharmacopoeia referred to above if available

☐ Yes ☐ No

- Attach a copy of the FPP manufacturer internal API(s) specifications in Annex L.
- If analytical methods are in-house, different from BP, USP and Ph.Int., attach a copy of the analytical method and analytical validation data in Annex M.

For sterile API:

Please provide the data on validation of the sterile aspects of the product including recent media fill validation data, as applicable, in Annex N.

Describe the method of sterilization used when applicable:

_____

_____

2.1.3 Certificate of analysis

Please provide a copy of the certificate of analysis of the API from the API manufacturer as well as from the finished pharmaceutical product (FPP) manufacturer in Annex O.

2.1.4 Suitability of monograph for API

Are you in a possession of the following information for APIs?

Certificate of suitability to the monograph of the European Pharmacopoeia (CEP): please attach a copy of the CEP and its annexes (Annex P).

Certificate No.: _____

2.1.5. Open part of drug master file (DMF) registered in (country):

_____

_____

Technical file (please attach):

☐ Yes ☐ No

Section 3: Finished pharmaceutical product

3.1 Manufacturing site GMP status

GMP inspections carried out by an NMRA

	NRA of country of origin	Any other inspection of PIC/S member	
GMP certificate no.			
Valid until			
Country			

Please attach the recent/valid GMP certificates/letter (Annex Q)

Other GMP inspections carried out by (include information for all that apply):

Agency	Date of audit	Outcome
WHO Prequalification Programme		
UNICEF Supply Division		
MSF International		
ICRC		
Other (specify)		

3.2 Finished pharmaceutical product specification

Standard	Edition	Year published
BP		
USP		
Ph.Int.		
In-house	Year documented	
Specifications additional to those in the pharmacopoeia referred to above (e.g. dissolution, syringeability) explain:		
Other (specify)		

Please attach copies of release and shelf-life specifications for the FPP in Annex R. If analytical methods are in-house, different from BP, USP and Ph.Int., attach a copy of the analytical method and analytical validation data in the same Annex R.

➢ Please attach a copy of the certificate of analysis for the three last batches released in Annex S.

3.3 Method of manufacture and process validation:

➢ Have the manufacturing methods for each standard batch size been validated?

☐ Yes ☐ No

If no, please clarify:

_____

_____

If yes, please provide details of validation status in the table below:

The batch size of the validated batches	
The batch numbers of the validated batches	
Manufacturing dates of the validated batches	
Reference number for the process validation report	
If processes are yet to be validated, the reference number for the process validation protocol should be indicated	

Provide batch formulae for all proposed batch sizes:

_____

➢ Please provide in Annex T a flow diagram and brief narrative describing the manufacturing and control process of this product with relevant parameters.

3.3.1 Additional information for sterile products

➢ Provide the data on validation of the sterile aspects of the product including recent media fill validation data as applicable in Annex U.

➢ Describe the method of sterilization used if applicable:

_____

3.4 Stability of finished product

3.4.1 Is stability testing data available?

☐ Yes ☐ No

Please provide the protocol and the report for accelerated and long-term stability testing, including: type and material of container; conditions (temperature/relative humidity/duration of stability study); number of batches involved in the study (minimum three); batch sizes for each lot tested; date of beginning of the study; and study conclusions. (These can be provided in Annex V.)

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

☐ Yes ☐ No

If no, describe the differences:

_____

_____

3.4.3 Please specify whether stability studies have been done or are ongoing with all declared API sources:

☐ Yes ☐ No

Submit a declaration in Annex W that stability studies have been done or are being done with all declared API sources.

If no, explain why:

_____

_____

3.4.4 Do you have ongoing stability data for this product?

☐ Yes ☐ No

Attach status report of any ongoing stability studies in Annex X.

3.4.5 Shelf-life as it appears on packaging:

☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years

Other (please specify): _____

3.4.6 Specific storage conditions for this product as they appear on the packaging and based on stability studies (e.g. "Do not store above 30 °C – Protect from light"):

Temperature	
Light	
Humidity	
Other (specify)	

3.4.7 Product suitable for use in:

- ☐ Zone I
- ☐ Zone II
- ☐ Zone III
- ☐ Zone IVa
- ☐ Zone IVb
- ☐ Other (please specify): _____

3.4.8 For oral powder for suspension and powder for injection, or injection that may be further diluted, or multidose containers provide in-use stability data and storage conditions after reconstitution and/or dilution in Annex Y.

Indicate the period (hours/days) until which the product is stable after reconstitution and/or dilution based on the available in-use stability data:

☐

Section 4: Safety/efficacy and/or therapeutic equivalence

(WHO Technical Report Series (TRS), No. 902, Annex 11/ TRS No. 937, Annex 7 or later)

4.1 For innovator products

Please attach a summary of pharmacology, toxicology and efficacy of the product in Annex Z.

4.2 For generic products: therapeutic equivalence

- ☐ Demonstrated
- ☐ Not demonstrated
- ☐ Not relevant, please explain why: _____

If demonstrated,

4.2.1 **By in vivo bioequivalence studies**

Study period (dd/mm/yyyy): from ☐ to ☐

Reference product

Generic name:	
Dosage form:	
Strength:	
Brand/trade name:	
Manufacturer:	
Manufacture site:	
Batch number:	
Expiry date:	

Study protocol

Contract research organization (CRO) name:	
Country of study:	
Number of volunteers:	
Study design (describe in detail):	

Bio batch size:	
Bio batch number:	
Bio batch API(s) source(s):	
Study conclusion:	

Study results:

Study conclusion:

4.2.2 By comparative in vitro dissolution tests according to conditions described in WHO BCS classification document (WHO Technical Report Series, No. 937, or later)

☐ Yes

☐ No (explain): _____

Reference product

Generic name	
Dosage form	
Strength	
Brand/trade name	
Manufacturer	
Manufacture site	
Batch number	
Expiry date	

Name and contact details of laboratory performing tests:

Study results

F2 (similarity factor) value (standard 50–100%):

F1 (difference factor) value:

Study conclusion:

4.2.3 By another method (please describe study conclusion briefly):

Attach graphic/pictorial representation of summary study results in Annex AA.

4.3 **The product used in the therapeutic equivalence study is essentially the same as the one that will be supplied (same materials from the same suppliers, same formula and same manufacturing method):**

☐ Yes

☐ No (explain what the differences are and justify that the differences do not have any impact on the bioavailability): _____

_____

_____

➢ Provide a copy of the report of the proof of therapeutic equivalence (BE study) comparative dissolution profile, dissolution tests, and others, if any, in Annex AB.

➢ For bioequivalence studies, indicate the stringent regulatory authority (SRA)/ WHO/PIC/S inspection status of the CRO (if the CRO has ever undergone inspections in relation to the current or other studies).

_____

_____

_____

➢ Attach schematic representation of study design (Annex AC)

➢ Attach study protocol summary (Annex AD)

Section 5: Commitment and authorization

5.1 **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, select the appropriate box below)

☐ 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)

If any changes occur to the information after the submission of this product questionnaire, the manufacturer/supplier undertakes to provide the relevant update as soon as possible.

Date: _____ Signature: _____

5.2 Power of attorney

The manufacturer authorizes a distributor to submit the questionnaire

Date: _____ Signature: _____

Distributor (Signed by Distributor for Manufacturer under power of attorney)

Please provide a copy of the power of attorney (Annex AE).

5.3 Authorization for sharing information with other agency

I, the undersigned confirm that the company has no objection to the information contained herein being shared with the agencies listed on page 2 (1.5) except:

_____

_____

I, the undersigned, certify that the information provided above is accurate, correct, complete, up-to-date and true at the time of submission.

Full name:

_____

_____

Full title/position in company:

_____

_____

Company name:

Signature

Date

Company seal/stamp:

Section 6: Attachments/annexes

Attachments or Annexes to the questionnaire should be in PDF format and should be well indexed to facilitate review

Please ensure that all documents necessary to enable objective evaluation of your product are attached. This checklist may not be exhaustive.

- ☐ A. Formulation of the product (complete qualitative and quantitative composition including active ingredient(s) and excipients (1.1.7)
- ☐ B. Description and composition of primary packaging materials (1.2.1)
- ☐ C. Description and composition of secondary packaging materials (1.2.2)
- ☐ D. Copy of product registered and currently marketed – Licence no. (1.6.1)
- ☐ E. Certificate of pharmaceutical product (CPP) according to the WHO Certification Scheme (WHO Technical Report Series, No. 863). An earlier version is not acceptable) (1.6.1)
- ☐ F. Submit recent as well as historical deficiency/acceptance letters issued by PQP/SRA in relation to the specific product dossier (1.6.1)
- ☐ G. Copy of the relevant WHO Prequalification approval letter signed by your company (1.6.3)
- ☐ H. WHO acceptance letter for product dossier review mentioning the WHO reference number assigned by WHO for this specific product (1.6.4)
- ☐ I. Package insert/leaflet (1.7.1)
- ☐ J. Patient information leaflet (1.7.4)
- ☐ K. GMP certificate from the country of origin (2.1.1)

- ☐ L. Attach a copy of the internal API(s) specifications (2.1.2)
- ☐ M. Validated analytical methods if analytical methods for finished product are in-house analytical method, different from BP, USP and Ph.Int. (2.1.2)
- ☐ N. Please provide the data on validation of the sterile aspects of the product including recent media fill validation data, as applicable (2.1.2)
- ☐ O. Copy of the certificate(s) of analysis of the API from the API manufacturer as well as from the FPP manufacturer (2.1.3)
- ☐ P. Copy of the certificate of suitability to the European Pharmacopoeia (CEP) and its annexes (2.1.4)
- ☐ Q. Recent/valid GMP certificates/letter (3.1)
- ☐ R. If specifications are in-house specifications, different from BP, USP and Ph.Int., attach copy of the in-house finished product specifications and also validated analytical methods (3.2)
- ☐ S. Copy of the certificate of analysis for the three last batches released (3.2)
- ☐ T. Flow diagram and brief narrative describing the manufacturing and control process of this product with relevant parameters (3.3)
- ☐ U. Data on validation of the sterile aspects of the product including recent media fill validation data as applicable (3.3.1)
- ☐ V. Protocol and report for accelerated and long-term stability testing (3.4.1)
- ☐ W. Submit a declaration that stability studies have been done or are being done with all declared API sources (3.4.3)
- ☐ X. Attach status report of any ongoing stability studies (3.4.4)
- ☐ Y. For oral powder for suspension and powder for injection, provide in-use stability data and storage conditions after reconstitution (3.4.8)
- ☐ Z. Please attach a summary of pharmacology, toxicology and efficacy of the product (4.1)
- ☐ AA. Attach graphic/pictorial representation of summary study results (4.2.3)
- ☐ AB. Provide a copy of the report of the proof of therapeutic equivalence (BE study) comparative dissolution profile, dissolution tests, and others if any (4.3)
- ☐ AC. Schematic representation of study design (4.3)
- ☐ AD. Study protocol summary (4.3)
- ☐ AE. Copy of the power of attorney (5.2)

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 re- quired 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.

	Distribution		Retrieval	
Name	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	

Table *continued*

Name and address of manufacturer (and if appropriate of supplier) of the active pharmaceutical ingredient			
Date of submission			
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, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, 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

	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 physicochemical 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		

Table *continued*

	YES	NO
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		
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		

Table *continued*

	YES	NO
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		
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

[1] Product 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

Table *continued*

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

Table *continued*

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

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/

Appendix 9

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 email 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		

Table *continued*

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:	
email:	

Contact person (quality issues):

Name:	
Telephone no.:	
Fax:	
email:	

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 10

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/ Manufac-turer	Manu-facturing site	Country	Sample

Addendum B: Manufacturer information

1. General information

Name	
Physical address of head office	
Postal address	
Telephone number	
Fax number	
Contact person	
Email 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	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	
Email	

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 11

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, inform 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.

	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: 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 12

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;
- 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 13

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	

Table *continued*

Points to check	Notes
Simulate process with media (not freeze) Smoke test (transport area) Transport Frequent fill volume Pre-cooling of shelves (no ice)	
Freezing Cycle Rate – (slow = crystals, polymorphism) Manner Drying temp. < eutectic point Determine eutectic point, consistent Shelf loading variations *Validate:* 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 14

Guidance on good manufacturing practices: model inspection report

Model inspection report

Section 1. General information

Name of organization:	
Website (link):	
Physical address:	
Postal address:	
Tel.:	
Fax:	
Contact person:	
Email address:	
Activities:	Prequalification ☐ Purchasing ☐ Receiving and storage ☐ Distribution ☐ Reassessment ☐
Date of assessment/inspection (dd/mm/yyyy):	
Products and/or product category (e.g. pharmaceuticals, diagnostics, medical devices)	
Name of inspector:	

Section 2. Summary

General information about the procurement agent and site
History of inspections
Focus of the inspection and areas inspected
Summary of findings
General activities:
Prequalification:
Purchasing:
Receiving and storage:
Distribution (including the ability to supply the needed products in quantities required):

Table *continued*

Reassessment:

Section 3. Observations and deficiencies/noncompliance

Note: Module I should be used in all cases of assessment of a procurement agency. Modules 2 to 6 may be used depending on the activities performed by the procurement agency.

	Module I: General requirements	Classification (C, M, O)
1.		
2.		
3.		
4.		
5.		
	Module II: Prequalification	
6.		
7.		
8.		
9.		
10.		
	Module III: Purchasing	
11.		
12.		
13.		
14.		

Table *continued*

	Module IV: Receiving and storage	
15.		
16.		
17.		
18.		
	Module V: Distribution	
19.		
20.		
21.		
22.		
	Module VI: Reassessment	
23.		
24.		
25.		
26.		

(C) Critical observation: An observation relating to any activity, action or omission thereof, by the procurement agency, in relation to product(s), that may result in a significant risk to the user.

(M) Major observation: A non-critical observation that:

- may have a negative impact on a product in relation to prequalification, purchasing, storage, distribution or requalification; and/or
- indicates a major deviation from the model quality assurance system (MQAS); and/or
- consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such.

(O) Other observation: An observation that cannot be classified as either critical or major, but indicates a departure from the recommendations in the MQAS (including good storage practices (GSP) and good distribution practices (GDP)).

Section 4. Outcome of the inspection *(select one of the following options)*

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the observations listed above – the agency was considered to be operating in compliance with the MQAS for the following activities (select the appropriate one(s)) prequalification, purchasing, storage, distribution, requalification).

Or

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the observations listed above – the agency was considered not yet to be operating at an acceptable level of compliance with the MQAS for the following activities (select the appropriate one(s)) prequalification, purchasing, storage, distribution, requalification). The corrective and preventive actions (CAPAs) will be reviewed after which a conclusion will be made as to whether the procurement agency is operating in compliance with the MQAS. (A reinspection may be considered before the conclusion is reached.)

Or

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the observations listed above – the agency was considered to be operating at an unacceptable level of compliance with the MQAS for the following activities (select the appropriate one(s)): prequalification, purchasing, storage, distribution, requalification).

Signature: _____ Date: _____

(Name): _____
(Print)

Appendix 15

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 16

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