WHO, UNICEF, UNAIDS and several other UN organizations are involved in the procurement of drugs. Without a documented quality system in place, organizations could risk sourcing sub-standard, counterfeit and/or contaminated medicines, leading to product complaints and product recalls, waste of money, and most seriously, health risks to patients.

WHO is currently undertaking a pilot project which will be used as a model for sourcing pharmaceuticals for other priority diseases. WHO will draft a model quality assessment system for procurement organizations through continued liaison with the relevant organizations.

This procedure for assessing the Acceptability, in Principle, of Pharmaceutical Products for Purchase by United Nations Agencies is considered to form the basis of the quality assessment system for procurement of pharmaceuticals.

©World Health Organization 2001

1) The procedure was adopted by the 37th WHO Expert Committee on Specifications for Pharmaceutical Preparations meeting held in Geneva 22-26 October 2001, and is included in its report TRS908 (Annex 8).
Contents

1. Introduction .................................................................................................................. 3
2. Steps of the procedure ................................................................................................. 4
   2.1 Publication of Invitation for Expression of Interest (EOI) .................................. 4
   2.2 Submission of Dossiers ....................................................................................... 4
   2.3 Screening of dossiers submitted ........................................................................... 6
   2.4 Dossier assessment ............................................................................................... 6
   2.5 Site Inspection ...................................................................................................... 6
   2.6 Report and outcome of evaluation ...................................................................... 7
   2.7 Assessment results ............................................................................................... 7
   2.8 Procurement, sourcing and supply ...................................................................... 8
   2.9 Re-evaluation ...................................................................................................... 8
   2.10 Testing of samples ............................................................................................. 8
   2.11 Monitoring of Complaints .................................................................................. 9
   2.12 Cost Recovery .................................................................................................... 9
   2.13 Confidentiality Undertaking ............................................................................. 9
   2.14 Conflict of Interest ........................................................................................... 10

Annex .................................................................................................................................. 11

References ........................................................................................................................ 13
1. Introduction

The World Health Organization (WHO) could provide United Nations agencies advice on the acceptability, in principle, of pharmaceutical products which are found to meet WHO recommended quality standards, for purchase by such UN agencies. This will be done through a standardized quality assessment procedure.

The purpose of the quality assessment procedure is to evaluate whether the pharmaceutical products meet the requirements recommended by WHO for multisource (generic) pharmaceutical products as appropriate\(^1\) and are manufactured in compliance with Good Manufacturing Practices (GMP)\(^2\).

The quality assessment procedure established by WHO is based on the following principles:

- Reliance on the information supplied by the National Drug Regulatory Authority (DRA);
- General understanding of the production and quality control activities of the manufacturers;
- Evaluation of product information submitted by manufacturers including product formulation, manufacture and test data and results;
- Assessment of consistency in production and quality control through compliance with GMP;
- Random sampling and testing of drugs supplied;
- Distribution of products;
- Handling of complaints and recalls;
- Monitoring of complaints from agencies and countries\(^1\).

WHO could also collaborate with DRAs in the quality assessment. WHO recommends that manufacturers expressing interest to supply drugs through the UN agencies inform the DRAs of their intention and request the DRA to collaborate with WHO in the quality assessment process. It is recommended that the manufacturers provide the DRA with the necessary authorization to discuss the relevant product files with WHO representatives during inspections where relevant or required (subject to appropriate confidentiality provisions, if necessary.

WHO will advise UN agencies of the manufacturers whose products have been found acceptable in principle for procurement through a procedure of quality assessment based on WHO recommended guidelines and standards.

12-12-2002
2. **Steps of the procedure**

WHO requires information related to the manufacturing and control of the products, and the manufacturing and testing companies. Interested manufacturers provide this information by submitting a product file with the required information, and information as requested about the manufacturing company. In addition to the evaluation of the product information submitted, a manufacturing site inspection(s) may be performed. The WHO reserves the right to terminate the quality assessment procedure of a manufacturer when the manufacturer is not able or fails to provide the required information in a specified time period, or when inadequate information is supplied to complete the quality assessment effectively.

### 2.1 Publication of Invitation for Expression of Interest (EOI)

WHO will publish an invitation widely in the international press and on the web pages at regular intervals when necessary for specific groups of products, to request manufacturers to submit an Expression of Interest (EOI) to supply pharmaceutical products to UN agencies. The invitation should be open and transparent, inviting all manufacturers to submit the EOI for the drugs listed in the invitation.

Manufacturers should submit their EOI with the relevant information requested, before the date specified by WHO.

WHO will receive the EOI and record the receiving of EOI from each manufacturer. Guidelines developed for the submission of the Dossiers shall then be sent to the interested manufacturers.

### 2.2 Submission of Dossiers

Each interested manufacturer should provide the focal point indicated in the EOI with a dossier containing the required information, before a specified date as determined by WHO.

The information should be submitted in the format reflecting the information summarized below. Alternatively, a standard dossier as prepared for or submitted to the DRA can be submitted, provided that it contains the information as required. In such cases, a covering letter cross-referencing the information should be provided by the manufacturer.

The following aspects must be covered:

For innovator products (from manufacturers whose products are manufactured and registered in a country with a stringent drug regulatory authority, including *inter alia* USA, EU/EEA and Japan):
a) A WHO-type Certificate of a Pharmaceutical Product\textsuperscript{2} issued by one of the regulatory authorities of ICH regions together with the summary of product characteristics (SmPC).

b) Assessment report(s) issued by the respective DRA.

c) WHO-type batch certificate from the manufacturer.

d) In case the packaging of the product is different from the one approved by the drug regulatory authorities of the ICH regions, then stability testing data should be submitted.

e) In case the formulation, strength, specifications, etc. are different from the product for which the WHO-type Product Certificate(s) was issued, arguments and/or data to support the applicability of the certificate(s) despite the differences should be submitted.

For multisource (generic products); the data and information to be submitted shall be as described in "Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products. A Manual for a Drug Regulatory Authority. Regulatory Support Series, No.5 (WHO/DMP/RGS/98.5). Geneva, World Health Organization, 1999"; including (as summarized below)

a) Details of the product.

b) Regulatory situation in other countries.

c) Active pharmaceutical ingredient(s) (API):
   (i) Properties of the active pharmaceutical ingredient(s),
   (ii) Sites of manufacture
   (iii) Route(s) of synthesis,
   (iv) Specifications:
      API described in a pharmacopoeia,
      API not described in a pharmacopoeia,
   (v) Stability testing.

d) Finished product:
   (i) Formulation,
   (ii) Sites of manufacture,
   (iii) Manufacturing procedure,
   (iv) Specifications for excipients,
   (v) Specifications for the finished product,
   (vi) Container/closure system(s) and other packaging,
   (vii) Stability testing,
   (viii) Container labelling,
   (ix) Product information,

\textsuperscript{2} The WHO type certificate of a Pharmaceutical Product refers to the certificate issued by the international drug regulatory authority in accordance with the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. Further information, and the full text of the WHO document "Guidelines on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce" can be found in the web site \url{http://www.who.int/medicines/}.
2.3 Screening of dossiers submitted

Each dossier submitted by the manufacturer will be screened for completeness prior to the evaluation of the dossier.

Dossiers that are incomplete will not be considered for evaluation. The manufacturer will be informed that an incomplete dossier has been received, and be requested to complete the dossier within a specified time period. In the event this is not complied with, the dossier will in principle be rejected on grounds of incompleteness and returned to the manufacturer.

Dossiers that are in compliance with the requirements of the WHO will be (a) retained for evaluation purposes and (b) the manufacturing site will be considered for a possible manufacturing site inspection (i.e. if warranted based on the outcome of the evaluation of the dossier).

2.4 Dossier assessment

The dossiers will be evaluated by a team of experts appointed by the WHO in the field of pharmaceutical development, pharmaceutics, bio-equivalence and other appropriate related fields. Evaluators will be appointed in accordance with a Standard Operating Procedure (SOP) established by WHO for appointment of evaluators of product information, and will be from Regulatory Authorities. The evaluation will be done in accordance with an SOP established by WHO for assessing product files based on the WHO guidelines to ensure uniformity in evaluation.

WHO will give technical support for the evaluation of product information supplied, if required.

2.5 Site Inspection

Dependent on the outcome of the evaluation of the product dossier, WHO will plan and co-ordinate performance of inspections at the manufacturing sites to assess compliance with Good Manufacturing Practices as recommended by WHO (2). The inspection will be performed by a team of inspectors consisting of experts appointed by WHO, preferably from Regulatory Authority Inspectorates. The experts will be of three main areas including production, quality control and GMP. A WHO staff member will co-ordinate the team and the team members will act on a temporary basis as expert advisers to WHO. The team(s) will perform the inspections and report on the findings in accordance with SOP's established by WHO for planning and performing site inspections to ensure a standard harmonized approach. The WHO GMP checklist will be used during the inspection.

12-12-2002
A representative(s) of the DRA of the country of manufacture would normally be expected to accompany the team to the manufacturing and testing facility to assess the compliance with GMP.

Evaluators and inspectors must have the relevant qualifications and experience.

2.6 Report and outcome of evaluation

The evaluators and inspection team(s) will finalize a report according to the established WHO format describing the findings and including recommendations to the manufacturers. This will be communicated to the manufacturers.

If any additional information is required, or corrective action has to be taken by the manufacturer, WHO will postpone its final recommendations until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified standards.

In the event of any disagreement between a manufacturer and WHO, an SOP established by WHO for the handling of appeals and complaints will be followed to discuss and resolve the issue.

As WHO is responsible for the quality assessment, the ownership of the reports lies with WHO (without prejudice, however, to any confidential and proprietary information of the manufacturer contained in this report).

2.7 Assessment results

Once WHO is satisfied that the quality assessment process is complete for the manufacturer of the relevant product and that the product is acceptable in principle for procurement by UN Agencies (i.e. it has been found to meet the WHO recommended standards), the product, as produced at the specified manufacturing site, will be included in the list.

Manufacturers on the list will be considered to be manufacturing the relevant listed pharmaceutical products, of acceptable quality, and in compliance with WHO recommended GMP guidelines and other recommended standards, such as described in "Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products. A Manual for a Drug Regulatory Authority. Regulatory Support Series, No.5 (WHO/DMP/RGS/98.5). Geneva, World Health Organization, 1999. The quality assessment is valid only for those product(s) submitted by the manufacturer in the EOI, evaluated by WHO, and appearing on the list.

Each manufacturer receives a letter from WHO informing the manufacturer of the outcome of the quality assessment process in regard of the particular product(s) of that particular manufacturer. A copy of this letter will be sent to the DRA of the country of manufacture.

12-12-2002
The list will be compiled in accordance with an SOP established by WHO for final decision making for inclusion in the list and will be subjected to review at least once a year. The list will be published and be included on the WHO web page.

2.8 Procurement, sourcing and supply

The WHO quality assessment procedure shall be independent from procurement. The UN agencies may use the list to guide them in sourcing of pharmaceutical products.

2.9 Re-evaluation

i. Re-qualification should be done at regular intervals.

ii. Suppliers will be required to communicate changes that may have impact on the safety, efficacy or quality of the product, to WHO.

iii. Re-inspections of manufacturers will be done at regular intervals at least once every 3 years.

iv. Change to key personnel or the manufacturing site could also result in a re-inspection.

v. Re-evaluation of dossiers will be done every 3 years, or sooner should any change regarding the formula, manufacturing method, or manufacturing site be implemented by the manufacturer.

Re-evaluation may also be done in the following situations:

- If any fraud or omissions by the manufacturer in the initial assessment procedure or during the follow-up activities is evident in relation to the requirements, including compliance with the Good Manufacturing Practices (GMP), recommended by the WHO.

- If any batch or batches of supplied product(s) are considered by WHO or one or more of the UN agencies or organizations not to be in compliance with the agreed specification of the product;

- If a complaint considered to be serious in nature has been received by the WHO or one or more of the UN agencies or organizations;

- If suspension of supply is equal to or greater than one year;

- If, in the opinion of the WHO, changes made in the sourcing of the Active Pharmaceutical Ingredients (API), formulation, manufacturing method, facility or other production aspects require that a re-assessment be made.

2.10 Testing of samples

Random samples of pharmaceutical product(s) supplied by listed suppliers, will be taken for independent testing of final product characteristics. Certificates of Analysis of final products released by the manufacturer and specifications for test methods should be provided by the manufacturer to the WHO, for review, on request.

12-12-2002
In the event of failure to meet the established criteria for re-evaluation and testing, WHO will investigate the problem and communicate this to the manufacturer.

2.11 Monitoring of Complaint(s)

Complaint(s) concerning a pharmaceutical product(s) or batch of product(s) supplied by the manufacturer, communicated to WHO, will be investigated in accordance with an SOP established by WHO.

After investigation, WHO will provide a written report of the problem and include recommendations for action where relevant.

A copy of the report will be sent to the DRA of the country where the manufacturing site is located. The DRA could be invited to participate in the investigation of the complaint.

WHO will make a copy of the report available to the manufacturer.

2.12 Cost Recovery

WHO reserves the right to charge for the quality assessment procedure on a cost recovery basis.

2.13 Confidentiality Undertaking

The evaluators and inspectors will treat all information to which they will gain access during the evaluations and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned project, as 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 evaluators of product dossiers and inspectors (team members participating in site visits) within the scope of the quality assessment procedure of pharmaceutical products.

Evaluators and inspectors will take all reasonable measures to ensure

(a) that confidential information is not used for any other purpose than the evaluation/inspection activities described in this document, and

(b) that it 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

12-12-2002
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.

2.14 Conflict of Interest

Before undertaking the work, each evaluator and inspector will also (in addition to the above mentioned confidentiality undertaking) be required to sign a Declaration of Interest. If based on this Declaration of Interest, it is felt that there is no risk of a real or perceived conflict of interest and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each evaluator and inspector is required to confirm that the information disclosed by him/her in the Declaration of Interest is correct and that no situation of real, potential or apparent conflict of interest is known to him/her, including that he/she has no financial or other interest in, and/or relationship with a party, which:

(a) may have vested commercial interest in obtaining access to any Confidential Information disclosed to him/her in the course of the evaluation/inspection activities described in this document; and/or

(b) may have a vested interest in the outcome of the evaluation activities/inspection including, but not limited to, parties such as the manufacturers whose products are subject to evaluation or manufacturers of competing products.

Each evaluator and inspector will undertake to promptly advise WHO of any change in the above circumstances, including if an issue arises during the course of his/her work for WHO.

All inspectors furthermore agree, that at the manufacturer’s request, WHO will advise the manufacturer in advance of the identity of each inspector and composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to WHO prior to the visit. If such concerns cannot be resolved in consultation with WHO, the manufacturer may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the manufacturer within ten days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel its agreement with the inspector, and the activities to be undertaken by that inspector, in whole or in part.
ANNEX

PROVISIONS FOR EVALUATORS OF PRODUCT DOSSIERS 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 the Performance of Work (APW), you will gain access to certain information, which is proprietary to WHO or entities collaborating with WHO, including the manufacturers of the product(s) which need to be assessed as part of the quality assessment procedure by WHO. You undertake to treat such information (hereinafter referred to as “the Information”) as confidential and proprietary to WHO or the aforesaid parties collaborating with WHO. In this connection, you agree:

(a) not to use the Information for any other purpose than discharging your obligations under the above-mentioned APW; and

(b) not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

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

(i) was known to you prior to any disclosure by or on behalf of WHO (including by the manufacturer(s)); or

(ii) was in the public domain at the time of disclosure by or on behalf of WHO (including the manufacturer(s)); or

(iii) becomes part of the public domain through no fault of your own; or

(iv) becomes available to you from a third party not in breach of any legal obligations of confidentiality.

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

You will discharge your responsibilities under the above-mentioned APW exclusively in your capacity as an expert adviser to WHO. In this connection, you confirm that the information

12-12-2002
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) _______________________________

Institute ________________________________________

Place ________________  Date _____________________
REFERENCES
