



**PREQUALIFICATION OF QUALITY CONTROL  
LABORATORIES. PROCEDURE FOR ASSESSING THE  
ACCEPTABILITY, IN PRINCIPLE, OF QUALITY CONTROL  
LABORATORIES FOR USE BY UNITED NATIONS AGENCIES.  
PROPOSAL FOR REVISION**

***DRAFT FOR COMMENTS***

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**SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/10.343:  
Prequalification of quality control laboratories. Procedure for assessing the acceptability, in  
principle, of quality control laboratories for use by United Nations agencies.  
Proposal for revision**

Need for revision identified by the Prequalification Programme (PQP)	January 2010
Draft prepared and discussed within PQP and by collaborating experts	January-February 2010
Draft mailed out for comments	March-April 2010
Review of comments received in consultation on Specifications for medicines and quality control laboratory issues	10-12 May 2010
Recirculation of revised draft	June-July 2010
Review of any comments received with subgroup	August-September 2010
Presentation to the WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Further action as necessary	...

## BACKGROUND

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted in its thirty-eighth report in 2003 the *Procedure for assessing acceptability, in principle, of quality control laboratories for use by United Nations agencies* (WHO Technical Report Series, No. 917, 2003, Annex 4). In 2006 the WHO Expert Committee adopted in its forty-first report a revised version of this procedure (*Prequalification of quality control laboratories. Procedure for assessing acceptability, in principle, of quality control laboratories for use by United Nations agencies*. WHO Technical Report Series, No. 943, 2007, Annex 5).

During the last three years the interest of quality control laboratories in prequalification has grown, the procedure has expanded and currently there are 12 prequalified laboratories and 39 laboratories have expressed the interest to be prequalified. The experience gained from implementation of the procedure and its extended use brought along the need for clarification of some issues, such as:

- possibility of use of outcomes of inspection and audit performed by an authority applying the standards at least equivalent to WHO-recommended quality standards for quality control laboratories;
- setting rules for priority assessment of interested quality control laboratories; and
- monitoring of performance of prequalified laboratories.

These amendments were also recommended for inclusion by the experts during an informal consultation on specifications for medicines and quality control laboratory issues held on 17-19 June 2007.

The recent revisions of the WHO guideline on *Good practices for pharmaceutical quality control laboratories* and the *Procedure for prequalification of pharmaceutical products* also induced the need for some amendments of the procedure for prequalification of quality control laboratories.

On the basis of the above the following text is proposed to replace the previously published procedure. It is presented in track-change mode in order to show the changes that have been made.

## Annex 5

Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies

### Introduction

#### 1. Steps of the procedure

- 1.1 Publication of invitation for Expressions of Interest
- 1.2 Submission of Expressions of Interest and laboratory information
- 1.3 Screening of submitted laboratory information
- 1.4 Evaluation of the laboratory information
- 1.5 Site inspection
- 1.6 Report and outcome of inspection
- 1.7 Results of assessment
- 1.8 Monitoring of prequalified quality control laboratories
- 1.9 Monitoring of complaint(s)
- 1.10 Cost recovery
- 1.11 Confidentiality undertaking
- 1.12 Conflict of interest

#### References

## INTRODUCTION

The World Health Organization (WHO) provides United Nations agencies, on request, with advice on the acceptability, in principle, of quality control laboratories that are found to meet WHO recommended quality standards for such laboratories, i.e. *Good Practices for Pharmaceutical Quality Control Laboratories (GPCL)* (1) and the relevant parts of good manufacturing practices (GMP) (2). This is done through a standardized quality assessment procedure. The purpose of the quality assessment procedure is to evaluate whether the quality control laboratories to be used for the analysis of pharmaceutical products meet the requirements recommended by WHO for such laboratories.

Participation in the prequalification procedure is voluntary and any pharmaceutical quality control laboratory (governmental or private) could participate. Certification such as ISO (in terms of ISO/IEC17025) is encouraged and will also be considered in the prequalification procedure. It is recommended that laboratories should work towards obtaining certification.

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

- a general understanding of the quality assurance management and quality control testing activities of the laboratory;
- evaluation of information submitted by the laboratory;
- assessment of compliance with WHO recommended quality standards for quality control laboratories, i.e. *GPCL* (1) and the relevant parts of GMP (2); and
- monitoring of performance of prequalified laboratories.

WHO should collaborate with national medicines regulatory authorities (NMRAs) in the quality assessment. WHO recommends that laboratories expressing their interest in testing medicines on behalf of United Nations agencies inform the regulatory authorities and other networks (e.g. the Official Medicines Control Laboratories (OMCL) network) of their intention to be prequalified and request the regulatory authorities to collaborate with WHO in the quality assessment process.

This procedure describes a process to be followed for prequalification of quality control laboratories for use by the United Nations agencies.

### 1. Steps of the procedure

WHO requires information related to the activities and quality control of pharmaceutical products in laboratories interested in being assessed under this procedure. Interested quality control laboratories should submit the information about their activities as requested by WHO (see point 1.2). In addition to the evaluation of the information submitted, a site inspection(s) may be performed.

If priorities have to be set for the assessment of interested laboratories, then priority will be given to national quality control laboratories and laboratories providing testing services to governments, and to quality control laboratories in areas where United Nations agencies identify the need for services in testing of quality of pharmaceutical products.

WHO reserves the right to terminate the quality assessment of a laboratory when the laboratory is not able, or fails to provide the required information and/or is unable to implement corrective actions which WHO may require within a specified time period, or when the information supplied is inadequate to complete the quality assessment effectively.

### 1.1 Publication of invitation for Expressions of Interest

WHO will publish, and when necessary repeat, an invitation to laboratories to submit an Expression of Interest (EOI) in testing pharmaceutical products as identified in the invitation on behalf of United Nations agencies. Such an invitation will be published widely, i.e. on the WHO web site and possibly also through other media, such as the international press. The invitation should be open and transparent, inviting all quality control laboratories to submit the EOI for prequalification.

### 1.2 Submission of Expressions of Interest and laboratory information

Each interested laboratory should provide the WHO focal point indicated in the invitation for EOIs with a letter expressing interest to participate in the prequalification procedure and the relevant laboratory information. WHO will record the receipt of the EOI from each laboratory in a register.

Guidelines for the submission of EOIs and for the preparation of the relevant information will be available on the WHO web site and be sent to interested laboratories upon request.

If the laboratory has documented its quality system as a quality manual this can be submitted, provided that it is supplemented with the information required for the laboratory information file (LIF, see below) that is not provided in the quality manual.

If there is no quality manual, the information should be submitted as described in the document *Guidelines for preparing a laboratory information file (LIF)* (3) and contain information on the areas listed below:

- general information on the laboratory, including activities proposed for prequalification;
- quality management system implemented, inspections and external audits performed in the laboratory;
- participation in proficiency testing schemes and/or collaborative trials;
- internal audits;
- control of documentation and records;

- personnel;
- premises;
- equipment;
- reagents, reference substances and reference materials;
- subcontracting of testing (where applicable);
- handling of samples;
- validation of analytical procedures;
- out-of-specification (OOS) result investigation;
- stability testing (where applicable); and
- microbiological testing (where applicable).

### 1.3 Screening of submitted laboratory information

The information submitted by the laboratory will be screened for completeness against the *Guidelines for preparing a laboratory information file* (3). Incomplete information will not be considered for evaluation. The laboratory will be informed that incomplete information has been received, and be requested to complete it within a specified time period. In the event of noncompliance with this request, the laboratory information will in principle be rejected on grounds of incompleteness and returned to the laboratory.

### 1.4 Evaluation of the laboratory information

Laboratory information that complies with the requirements set out in section 1.2 above will be evaluated in accordance with a standard operating procedure (SOP) established by WHO to ensure uniformity in evaluation of the information. The information will be evaluated against the WHO recommended quality standards for quality control laboratories, i.e. *GPCL (1)* and the relevant parts of GMP (2), and the laboratory will be considered for a possible site inspection.

A laboratory may submit a report from the inspection or audit performed by a regulatory authority applying standards at least equivalent to WHO recommended quality standards for quality control laboratories, i.e. *GPCL (1)* and the relevant parts of GMP (2), and a response to the inspection or audit. In this case, based on the assessment of the report and response, if the laboratory is considered to be operating at an acceptable level of compliance with WHO recommended standards, it may not be necessary for an initial site inspection to be performed by WHO.

### 1.5 Site inspection

Depending on the outcome of the evaluation of the laboratory information, WHO may plan and coordinate inspections of the laboratory to assess compliance with WHO recommended quality standards for such laboratories, i.e. *GPCL (1)* and the relevant parts of GMP (2)<sup>1</sup>. The inspection

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<sup>1</sup> Training modules can be found on the Prequalification web site (<http://www.who.int/prequal/>).

will be performed by an inspector, or a team of inspectors, having the relevant qualifications and experience. The inspectors may be WHO inspectors and/or experts appointed by WHO. A WHO staff member will coordinate the team and the team members will act as temporary expert advisers to WHO. The inspector or team will perform the inspections and report on the findings in accordance with SOPs established by WHO to ensure a standard harmonized approach.

A representative or representatives of the NMRA of the country where the laboratory is located would normally be expected to accompany the team to the laboratory to participate in the assessment of the laboratory's compliance with WHO recommended quality standards for quality control laboratories.

## 1.6 Report and outcome of inspection

The inspector or inspection team will finalize a report describing the findings according to the established WHO SOP and format. The report will be communicated to the laboratory and a copy will be sent to the relevant NMRA.

If any additional information is required, or if corrective action has to be taken by the laboratory, WHO will postpone its decision on the acceptability of the laboratory concerned until the additional information has been evaluated, or the corrective action has been taken and found satisfactory. If the decision cannot be made based on the information received a follow-up inspection will be performed.

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

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

## 1.7 Results of assessment

Once WHO is satisfied that the quality assessment process for the laboratory is complete, and that the laboratory is acceptable in principle for use by United Nations agencies (i.e. it has been found to meet the WHO recommended quality standards for quality control laboratories), the laboratory at the specified site will be included in a list referred to as "List of prequalified quality control laboratories".

Laboratories on the list will be considered to be able to test products in compliance with WHO recommended quality standards for quality control laboratories. Inclusion in the list does not, however, imply any approval by WHO of the laboratories (which is the sole prerogative of national authorities).

Each laboratory will receive a letter from WHO informing it of the outcome of the quality assessment process for that particular laboratory.

A copy of this letter will be sent to the NMRA of the country where the laboratory is located. The list of prequalified laboratories will be published on the WHO web site and will specify the areas of expertise assessed and considered prequalified. The list will be updated whenever new relevant information arises.

WHO will – subject to the protection of any confidential information – publish WHO Public Inspection Reports (WHOPIR(s)), in accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, on the laboratories considered to meet WHO recommended quality standards for quality control laboratories. These reports will be published on the WHO web site.

### 1.8 Monitoring of prequalified quality control laboratories

Once the laboratory is included in the list of prequalified quality control laboratories, it should inform WHO without delay about any implemented changes which may have significant impact on the prequalification of the laboratory (such as changes to facility, equipment or key personnel) and should submit the updated LIF.

Each prequalified quality control laboratory will be re-evaluated on a routine basis at regular intervals (annually or when information requiring re-evaluation is obtained).

To enable WHO to carry out re-evaluation all prequalified laboratories are requested to submit a brief annual report on their activities. The report should cover activities related to quality control of medicines within a calendar year and should be submitted by the end of March of the subsequent year. The following items should be included in the report:

- a summary of services provided to United Nations agencies, other organizations procuring medicines under international funding and other customers;
- a summary of number of samples analyzed, differentiating between compliant and non-compliant samples;
- list of analytical methods used;
- a summary of complaints concerning results of analysis performed by the laboratory received from customers;
- brief details of participation in proficiency testing schemes (organizing party, methods involved, outcomes and, if appropriate, adopted corrective measures);
- listing of inspections and audits performed by external parties, identifying the party and scope of the inspection and audit; and
- in the case that changes have been implemented, which have significant impact on the content of the LIF, then a summary of these changes should be included in the report and an updated LIF should be attached.

Re-inspections of prequalified laboratories will be performed at a frequency based on risk assessment but at least once every five years. WHO reserves the right to proceed with the inspection of a prequalified laboratory any time, when considered necessary based on the information or complaint received.

WHO may suspend or withdraw a prequalified quality control laboratory from the List of prequalified quality control laboratories when there is evidence of non-compliance with the WHO recommended quality standards for such laboratories and/or this procedure.

### 1.9 Monitoring of complaint(s)

Complaint(s) concerning the results of analysis of pharmaceutical product(s) performed by the prequalified laboratory or concerning the service provided by the prequalified laboratory that are communicated to WHO, will be investigated in accordance with an SOP established by WHO.

After conducting its investigation, WHO will provide a written report of the problem and where appropriate include recommendations for action. WHO will make a copy of the report available to the laboratory under investigation and to the NMRA of the country where the prequalified laboratory is located. The NMRA could also be invited to participate in the investigation of the complaint.

### 1.10 Cost recovery

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

### 1.11 Confidentiality undertaking

The evaluators and inspectors will treat all information to which they gain access during the evaluation of the LIF 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 out below.

Evaluators and inspectors will take all reasonable measures to ensure that confidential information:

- is not used for any purpose other than the activities described in this document; and
- 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:

- (i) was known to them prior to any disclosure by or on behalf of WHO (including by laboratories); or

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

## 1.12 Conflict of interest

Before undertaking the work, each evaluator and inspector will (in addition to the above-mentioned confidentiality undertaking) be required to sign a Declaration of Interest in accordance with the terms set out below. If based on this Declaration of Interest, it is felt that there is no risk of a real or perceived conflict of interests and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he or she will discharge his or her functions exclusively as adviser to WHO.

In this connection, each evaluator and inspector is required to confirm that the information disclosed by him or her in the Declaration of Interest is correct and that no situation of real, potential or apparent conflict of interests is known to him or her, including that he or she has 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 him or her in the course of the evaluation or inspection activities described in this document; and/or
- may have a vested interest in the outcome of the evaluation or inspection.

Each evaluator and inspector will undertake to advise WHO promptly of any change in the above circumstances, including any issue which may arise during the course of his or her work for WHO.

All inspectors furthermore agree, that at the laboratory's request, WHO will advise the laboratory in advance of the identity of each inspector and the composition of the team performing the site inspection and provide curricula vitae of the inspectors. The laboratory 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 laboratory may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the laboratory within 10 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.

## References

1. Good practices for pharmaceutical quality control laboratories. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex X.
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2, Second updated edition. Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007.
3. Guidelines for preparing a laboratory information file. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 917), Annex 5).

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Draft for comments