Annex 3

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

Introduction

This document provides an update of the procedure originally published as Annex 12 in World Health Organization (WHO) Technical Report Series, No. 961, 2011. WHO provides United Nations (UN) agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States, on request, with advice on the acceptability, in principle, of quality control laboratories (QCLs) that are found to meet WHO-recommended quality standards for such laboratories. These standards are set out in *Good practices for pharmaceutical quality control laboratories* (GPCL) (*1*), and include, where applicable, good practices for pharmaceutical microbiology laboratories (*2*) and the relevant parts of good manufacturing practices (GMP) (*3*). This is done through a standardized quality assessment procedure. The purpose of the quality assessment procedure is to evaluate whether the QCLs to be used for the quality control of pharmaceutical products meet the requirements recommended by WHO for such laboratories.

Participation in the prequalification procedure is voluntary and any pharmaceutical QCL (governmental or private) providing quality control services for pharmaceutical products to UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States is eligible.

Accreditation, such as ISO (in terms of ISO/IEC17025), is encouraged and will also be considered in the prequalification procedure. Laboratories are recommended to work towards obtaining accreditation.

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

- evidence that the laboratory provides or is committed to offering quality control services for pharmaceutical products to UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States;
- a general understanding of the documented 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 QCLs, i.e. GPCL (*1*), including, where applicable, good practices for pharmaceutical microbiology laboratories (*2*) and the relevant parts of GMP (*3*);
- monitoring of performance of prequalified laboratories.

WHO invites the national medicines regulatory authority (NMRA), having regulatory oversight over a laboratory participating in the prequalification procedure, to join as an observer in the inspection of the laboratory's compliance with WHO-recommended standards for QCLs. WHO recommends that laboratories expressing an interest in participating in the prequalification procedure inform the regulatory authority of the country in which they are established as well as relevant networks (e.g. the official medicines control laboratories network) of their submission for prequalification.

This procedure is to be followed for prequalification of QCLs for use by UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States.

1. Steps of the procedure

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

If, due to insufficient resources and time constraints, WHO has to set priorities in the assessment of interested laboratories, then priority will be given to QCLs in areas where UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States identify the need for testing of the quality of pharmaceutical products.

Applications from laboratories that belong to or are affiliated with a manufacturer of pharmaceutical products, particularly those that have an interest in having one or more of their products prequalified by WHO or whose product(s) is/are already prequalified by WHO, may be given lower priority or may not be evaluated at all.

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

1.1 Publication of invitation for Expressions of Interest

WHO will publish an invitation to QCLs to submit an Expression of Interest (EOI) to participate in the prequalification procedure. Such an invitation will specify the scope of quality control testing which is subject to prequalification

and will be published widely, i.e. on the WHO website and possibly also through other media, such as the international press. The invitation will be open and transparent, inviting all interested QCLs to submit an EOI for prequalification.

1.2 Submission of EOIs and laboratory information

Each interested laboratory should provide the WHO focal point indicated in the invitation for EOIs with:

- a cover letter expressing interest in participating in the prequalification procedure;
- evidence that the laboratory provides, or is committed to offering, quality control services for pharmaceutical products to UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States; and
- the relevant laboratory information.

WHO will record the receipt of the EOI from each laboratory in a register. 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.

The information should be submitted as described in the document *Guidelines for preparing a laboratory information file* (*4*) and cover the areas listed below:

- general information on the laboratory, including activities proposed for prequalification;
- quality management system implemented, and 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 and/or verification of analytical procedures;
- investigation of out-of-specification (OOS) results;
- stability testing (where applicable);
- microbiological testing (where applicable).

Guidelines for the submission of EOIs and for the preparation and submission of the relevant information are available on the WHO website at http://apps.who.int/prequal/ and will be sent to interested laboratories upon request.

1.3 Screening of submitted laboratory information

The *Guidelines for preparing a laboratory information file* (*4*) will be used in an initial screening of the information supplied. The information will not be evaluated if it is not complete. In such cases the laboratory will be requested to provide additional information within a specified time. If the additional information is not received by the deadline, the application will be rejected.

1.4 Evaluation of the laboratory information

Laboratory information that complies with the requirements set out in section 1.2 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 QCLs, i.e. GPCL (*1*), including, where applicable, good practices for pharmaceutical microbiology laboratories (*2*) and the relevant parts of GMP (*3*), and the laboratory will be considered for a possible site inspection.

A laboratory may submit the report of the inspection or audit performed by a regulatory authority applying standards at least equivalent to WHO-recommended quality standards for QCLs, i.e. GPCL (*1*), including, where applicable, good practices for pharmaceutical microbiology laboratories (*2*) and the relevant parts of GMP (*3*), and the response of the laboratory to the observations made by the authority during inspection or audit.

Based on an SOP established by WHO for review of external inspections and audits, if the laboratory is considered to be operating at an acceptable level of compliance with WHO-recommended standards, WHO may decide that it is not necessary to conduct a site inspection.

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*), including where applicable good practices for pharmaceutical microbiology laboratories (*2*) and the relevant parts of GMP (*3*).[1] The inspection will be performed by an inspector, or a team of inspectors, having the relevant qualifications and experience in the field of quality control of pharmaceutical products.

External inspectors will be appointed in accordance with an SOP established by WHO and will act as temporary advisers to WHO. The external inspectors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure. A WHO staff member will coordinate the team. The inspector or inspection 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 having regulatory oversight over a laboratory participating in the prequalification procedure will be invited to accompany the team as an observer.

With a view to coordinating inspection activities, avoiding duplication and promoting information sharing without prejudice to the protection of any confidential and proprietary information of the laboratory in accordance with the terms of this procedure, WHO may disclose inspection-related information to regulatory authorities of WHO Member States, UN agencies and to the European Directorate for the Quality of Medicines & HealthCare.

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 by WHO to the laboratory and a copy will be sent to the NMRA having regulatory oversight over the laboratory.

If any additional information is required, or if a 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 such disagreements 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

[1] Training modules can be found on the WHO Prequalification website (http://apps.who.int/prequal/).

confidential and proprietary information of the laboratory contained in this report). Thus, WHO shall be entitled to use and publish such reports subject always, however, to the protection of any confidential and proprietary information of the laboratory. "Confidential information" in this context means:

- confidential intellectual property, "know-how" and trade secrets (including, e.g. programmes, processes or methods, unpublished aspects of trademarks and patents);
- commercial confidences (e.g. structures and development plans).

Provisions of confidentiality will be contained in the letters exchanged between WHO and the laboratory, to be agreed upon before the evaluation of the information and site inspection.

Notwithstanding the foregoing, WHO reserves the right to share the full reports with the relevant authorities of any interested Member State of the Organization and interested UN agencies.

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 UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States (i.e. it has been found to meet the WHO-recommended quality standards for QCLs), 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 QCLs. Inclusion in the list does not, however, imply any approval by WHO of the laboratories (which is the sole prerogative of national authorities).

Before publication of its name on the list of prequalified laboratories, 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 website and will specify the areas of expertise assessed and considered prequalified. The list will be updated whenever new relevant information is obtained.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will – subject to the protection of any confidential and proprietary information – publish WHO Public Inspection Reports on the laboratories considered to meet WHO-recommended quality standards for QCLs. These reports will be published on the WHO website.

1.8 Monitoring of prequalified QCLs

Once the laboratory is included in the list of prequalified QCLs, it should inform WHO without delay about the implementation of any changes that may have an impact on the prequalification of the laboratory (such as changes to facility, equipment or key personnel) and should submit an updated LIF.

Each prequalified QCL will be re-evaluated at regular intervals (annually) or earlier, when information indicating the necessity for re-evaluation is obtained by WHO.

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 all activities related to quality control of pharmaceutical products within the preceding three years 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 UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States;
- a summary of number of samples analysed, differentiating between compliant and noncompliant samples including any OOS/out-of-trend investigations;
- a list of analytical methods used;
- a summary of complaints received from customers concerning results of analyses performed by the laboratory;
- brief details of participation in proficiency testing schemes (organizing party, methods involved, outcomes and, if appropriate, corrective measures adopted);
- listing of inspections and audits performed by external parties, identifying the party and the scope of the inspection and audit;
- in the case that changes have been implemented, which have an impact on the content of the LIF, a summary of these changes should be included in the report and an updated LIF should be attached.

WHO will conduct re-inspections of prequalified laboratories in accordance with SOPs established by WHO. The frequency of such re-inspections depends on WHO's assessment of the quality risk management factors described below. Normally, however, such re-inspections will take place at least once every three years. The following factors will be taken into account when planning inspections:

- major changes, e.g. to premises, equipment or key personnel;

- the results of previous inspection(s)/audit(s) by WHO or another external party, and history of compliance of the laboratory with WHO-recommended quality standards;
- the outcomes of participation of the laboratory in proficiency testing schemes;
- number and significance of complaints made known to the QCL by customers;
- laboratory experience with testing of pharmaceutical products;
- WHO experience with testing services provided by the laboratory.

WHO reserves the right to proceed with the re-inspection of a prequalified laboratory at any time this is considered necessary based on information or complaints received by WHO. The NMRA that has regulatory oversight over the laboratory will be invited to participate in the re-inspection as an observer.

WHO may suspend or withdraw a prequalified QCL from the list of prequalified QCLs when there is evidence of noncompliance with the WHO-recommended quality standards for such laboratories and/or this procedure.

The re-evaluation of the prequalification status of a QCL may not be prioritized if the laboratory has not, for a continuous period of more than three years, provided quality control services for pharmaceutical products to UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States. In such cases, WHO will request the QCL to provide evidence that such services had been offered to, or commitments made to continue to offer such services, to UN agencies, their partners, procurement agencies serving national authorities and/or national authorities.

1.9 Monitoring of complaints

Complaints concerning the results of analysis of pharmaceutical products performed by the prequalified laboratory or concerning the service provided by the prequalified laboratory, which are communicated to WHO, will be investigated in accordance with an SOP established by WHO. The NMRA that has regulatory oversight over the laboratory will be invited to participate in the investigation of the complaint.

After conducting its investigation, WHO will provide a written report of the problem, which may, where appropriate, include recommendations for action to the laboratory under investigation and to the NMRA having the regulatory oversight over the laboratory.

1.10 Cost recovery

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

1.11 Confidentiality undertaking

WHO will require any external inspectors (acting as temporary advisers to WHO) to treat all information to which they gain access during the inspections of the laboratory, or otherwise in connection with the discharge of their responsibilities in regard to the prequalification procedure, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set out below.

Such inspectors will be required to take all reasonable measures to ensure that confidential information:

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

External 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 laboratories); or
- was in the public domain at the time of disclosure by or on behalf of WHO (including by laboratories); 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.

1.12 Conflict of interest

Before undertaking the work, each external 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 (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the inspector in question to undertake this work, he/she will discharge his/her functions exclusively as an adviser to WHO. In this connection, each inspector is required to confirm that the information disclosed by him/her in the declaration

of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All external 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 external inspectors. The laboratory then has the opportunity to express possible concerns regarding any of the external inspectors to WHO prior to the visit. If such concerns cannot be resolved in consultation with WHO, the laboratory may object to an external inspector's participation in the site visit. Such an objection must be made known to WHO by the laboratory within 10 days of being notified of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel its agreement with the inspector in question 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: Annex 1 (WHO Technical Report Series, No. 957).
2. WHO good practices for pharmaceutical microbiology laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 2 (WHO Technical Report Series, No. 961).
3. Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. WHO guidelines, good practices, related regulatory guidance and GXP training materials. Geneva: World Health Organization; 2016 (http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/, accessed 11 November 2016).
4. WHO guidelines for preparing a laboratory information file. Revision. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-eighth report. Geneva: World Health Organization; 2011: Annex 13 (WHO Technical Report Series, No. 961).