PREQUALIFICATION OF IN VITRO DIAGNOSTICS

WHO PROTOCOL FOR THE PERFORMANCE EVALUATION OF RAPID DIAGNOSTIC TESTS FOR DETECTION OF VIBRIO CHOLERAE LPS ANTIGEN
PQDx_305. Version: 1.0
3. Introduction

3.1. WHO Prequalification of In Vitro Diagnostics Programme

The World Health Organization (WHO) Prequalification of In Vitro Diagnostics is coordinated through the Prequalification Team - Diagnostics Assessment. The aim is to promote and facilitate access to safe, appropriate and affordable in vitro diagnostics (IVDs) including Point Of Care Tests (POCTs) of good quality in an equitable manner. Focus is placed on products intended for use in resource-limited settings.

The WHO prequalification of IVDs process comprises three components:

- review of product dossier;
- performance evaluation of the product;
- inspection of the manufacturing site(s).

This document pertains to the objectives and processes of the performance evaluation component of the prequalification assessment.

3.2. WHO performance evaluation of rapid diagnostic tests (RDTs) for detection of Vibrio cholerae Lipopolysaccharide antigen using stool specimens

The performance evaluation determines the accuracy of rapid diagnostic tests for detection of *Vibrio cholerae* (V. cholerae) Lipopolysaccharide (LPS) antigen in comparison with established reference methods. The evaluation characteristics include: accuracy (sensitivity, specificity, negative and positive predictive values), lot to lot variation and repeatability studies. In addition, a number of operational characteristics will be assessed including the suitability for use in laboratories and/or testing settings with limited infrastructure and other constraints.

RDTs for detection of *V. cholerae* LPS antigen submitted for performance evaluation will be assessed at WHO evaluating laboratory [institution name, and country] upon the instruction of WHO/PQT.

4. Study objectives

Overall objectives

The overall objective is:

1. To verify the performance of currently available RDTs for detection of *V. cholerae* LPS antigen against established WHO performance criteria.

4.1. Specific objectives

The specific objectives of the evaluation are:

1. To determine the sensitivity and specificity of currently available RDTs for detection of *V. cholerae* LPS antigen in freshly collected stool specimens as compared to reference methods including bacterial culture and detection of *V. cholerae* specific DNA sequences using Nucleic acid detection method (NAT).

2. To evaluate the operational characteristics of RDTs for detection of *V. cholerae* LPS antigen e.g. ease of use, inter-reader variability, reaction endpoint stability, rate of invalid runs/devices, and suitability for use in countries with limited infrastructure (no/limited electricity, no/limited clean water, and inadequate means of biosafety disposal).
5. Study Design

5.1. PQ evaluating Laboratory

[Institute name] has been identified as the WHO PQ Evaluating Laboratory for this performance evaluation. [Institute name] holds the following certification for quality management within the laboratory: ISO 15189:2012 (Medical laboratories — Particular requirements for quality and competence) or ISO 17025:2005 (General requirements for the competence of testing and calibration laboratories), issued by [certifying body name] or equivalent. [Insert PI name] will act as the Principle Investigator (PI).

5.2. Training, performance evaluation and supervision

The following issues are key to minimize errors and maximize the value of this evaluation:

- The PI will be responsible for training the laboratory staff on the evaluation protocol and on testing of each assay undergoing evaluation;
- Only those laboratory staff who have received specific assay training for the evaluation will be involved in the assessment;
- Accurate record keeping is crucial to the success of the evaluation and the PI will be responsible for ensuring that all data required for the evaluation are recorded on the agreed data collection sheets, and they are accurate, legible and up to date;
- It is important to plan work in advance and follow standard operating procedures as prepared and controlled by the WHO Evaluating Laboratory;
- To reduce the risk of adding an incorrect specimen to a test device or well, before starting the test run, the operator will prepare worksheets and label all tubes, dilution vessels, test devices or plates with the specimen’s unique number;
- Because objective, machine-generated, permanent results for subjectively read POC tests are not feasible, it is essential that the PI emphasizes to the operators performing the tests the need for accurate recording of results and record keeping;
- To minimize the risk of error, it is recommended that the results are read and recorded independently by three trained staff members;
- To allow immediate correction of erroneous recording of results (rather than differences in visual interpretation), the PI or designee should review the results within the range of time recommended by the manufacturer to allow him/her to return to the original test device to investigate apparently discordant readings;
- During each evaluation both positive and negative controls will be included and result will be recorded. Invalid test results will also be digitally recorded.

5.3. Safety

Cholera and other potential pathogens found in stool specimens are transmissible by contact. Therefore, all specimens must be handled as potentially infectious. Appropriate precautions to minimize infectious hazards must be taken at all stages from the collection of specimens to the disposal of used materials from the laboratory. The WHO Guidelines on Safety Precautions, and
Guidelines for the Safe Transport of Specimens (WHO/EMC/97.3) and the WHO Evaluating Laboratory Guidelines on Laboratory Safety shall be strictly adhered to by the laboratory staff.

5.4. Storage of assays

All reagents shall be stored as indicated in the assay instructions for use. Calibrated thermometers or other environmental monitoring devices will be placed at each location where reagents and specimens will be stored, i.e. ambient, refrigerator and freezer. Temperatures will be recorded daily. The lot numbers of the test kits received and used and their expiry dates will be recorded on the individual run worksheets.

Two separate production lots manufactured from different lots of critical reagents with different expiry dates will be requested for the performance evaluation, according to the following definition of a lot:\(^1\) “The amount of material that is uniform in its properties and has been produced in one process or series of processes. The material can be either starting material, intermediate material or finished product.” WHO will verify this information before the product assessment has been finalized.

6. Specimens

6.1.1. Ethical considerations

The PI will submit the protocol to the national institutional review board for scientific and ethical clearance before starting the evaluation. The study participants will include adult and children patients with watery diarrhea and suspected to have cholera infection. The specimens will include left-over stool specimens freshly collected in appropriate containers or rectal swabs depending on the manufacturer’s recommendations. The participants will be asked to provide informed consent before collection of the stool specimen. The collected left-over stool specimens will only be used to evaluate new assays if the clinical test results have been obtained and used for patient care where relevant. All individual identifiers will be removed and samples assigned unique identification numbers. None of the results generated from the assays being assessed will be used to determine the cholera infection status of the individual.

6.1.2. Collection of stool specimens

Freshly passed stool specimens will be collected using the device provided within the test kit or according to the assay’s instructions for use (IFU). Specific precautions and preservation for the particular specimen type shall be observed for each assay under evaluation.

To estimate expected sensitivity and specificity of 95%, with an error margin of 5% and 95% CI, a minimum of 88 \(V\) cholerae LPS antigen positive specimens and 88 \(V\) cholerae LPS antigen negative specimens will be required. However to increase the power of the study, minimum of 200 \(V\) cholerae LPS antigen positive and 500 \(V\) cholerae LPS antigen negative specimens will be included in the performance evaluation.

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\(^1\) ISO 18113-1:2009 In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) – Part 1: Terms, definitions and general requirements
6.1.3. Characterization of the cholera specimen panel

The freshly collected stool specimen which will be used in the performance evaluation shall be transported and stored according to the manufacturer’s instructions and then characterized using a standardized combination of assays i.e. a testing algorithm. These results will be used to determine the cholera status of each specimen for the purpose of the performance evaluation (see Figure 1). Use of any other combination of assays for characterization of the cholera specimen evaluation panel shall be communicated, discussed and agreed with WHO beforehand.

Initially, each specimen will be inoculated onto enrichment medium or directly onto Thiosulfate Citrate Bile-Salts Sucrose (TCBS) medium. The phenotypically characteristic colonies (large 2 to 4 mm in diameter), slightly flattened, shiny, yellow colonies with opaque centers and translucent peripheries), will be sub-cultured on a non-selective medium, followed by an oxidase test. Specific antisera will be used to differentiate *V cholerae* O1 and O139 from other enteric pathogens.

Specimens giving colonies with a characteristic *V. cholerae* phenotype, oxidase positive and agglutinating with specific cholera antisera will be assigned as cholera LPS antigen positive. Specimens that are negative on culture or are cholera antigen negative based on characteristic phenotype or agglutination, will be tested using TaqMan™ Vibrio cholera Assay (Applied Biosystems). Specimens that are culture and NAT negative for cholera will be assigned as cholera LPS antigen negative. Specimens that are culture negative but cholera NAT positive will be excluded from the evaluation panel.

![Figure 1 - WHO testing algorithm for detection of the *V. cholerae* O1 or O139 in stool specimens.](image-url)
7. Laboratory testing

7.1. Review of instructions for use

Each product under evaluation is used strictly in accordance with the instructions for use (IFU) issued by the manufacturer. The PQ Evaluating Laboratory will send a copy of the IFU to WHO/PQT upon delivery of the test kits and prior to commencement of the laboratory evaluation. The IFU shall be reviewed against the IFU submitted to WHO/PQT as part of the dossier assessment for the prequalification assessment. If the IFU has been updated since dossier submission, a letter detailing justification for changes made shall be sent to WHO/PQT prior to the laboratory evaluation commencing.

7.2. Sequence of testing

The WHO cholera specimen panel will be run such that approximately one half of the specimen panel will be run with one of the lots submitted, and the other half of the panel with the other lot. The freshly collected stool specimens which will be used in the performance evaluation of RDTs for detection of V. cholera LPS antigen will be tested singly in the assay under evaluation.

For the purpose of evaluating the rapid diagnostic tests, a ‘test run’ is defined as a consecutive run of tests of the same production lot performed during the same ‘session’. A ‘testing session’ might be considered to be a morning or afternoon.

7.3. Recording test results

All test results will be recorded on standardized test result worksheets and then entered in a Microsoft Excel spreadsheet for further data analysis. For subjectively read assays such as rapid diagnostic tests or line immunoassays, the intensity of the band, line or spot (very weak bands/medium to strong) is additionally entered into the data collection sheet (Table 2).

Table 2 - Results legend for data collection sheets for subjectively read assays

<table>
<thead>
<tr>
<th>Scoring index</th>
<th>RDT results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Non-reactive</td>
</tr>
<tr>
<td>1</td>
<td>Reactive (Very weak band)</td>
</tr>
<tr>
<td>2</td>
<td>Reactive (Medium to Strong Band)</td>
</tr>
<tr>
<td>7</td>
<td>Debris/invalid</td>
</tr>
</tbody>
</table>

Visual interpretation of results of subjectively read assays is made independently by operator and two more readers (without the knowledge of the others’ sets of results) and entered into the data collection sheets. When the three readers interpret the results differently from each other, the consensus is recorded as that interpretation which occurs two out of three times.

A technician’s appraisal is made of each assay under evaluation and is completed by the operator performing the testing as shown in Table 3 below.

Table 3 Technician appraisal of specific operational characteristics
<table>
<thead>
<tr>
<th></th>
<th>Rating*</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kit instructions:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Clarity</td>
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<td>Presentation</td>
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<td>Content</td>
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<tr>
<td>Safety instructions</td>
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<tr>
<td><strong>Kit/reagent packaging and labelling</strong></td>
<td></td>
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<tr>
<td>Clear</td>
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<td>Labelling</td>
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<tr>
<td>Safety</td>
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<tr>
<td><strong>Specimen dispensing and volume</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Specimen type used</td>
<td>Fresh stool/swab</td>
<td></td>
<td></td>
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<tr>
<td>Specimen volume ___ µL</td>
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<td></td>
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<tr>
<td>Specimen addition control</td>
<td></td>
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<tr>
<td><strong>Reagent dispensing</strong></td>
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<tr>
<td>Reagent addition control</td>
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<tr>
<td><strong>Equipment required</strong></td>
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<tr>
<td>Equipment required</td>
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<tr>
<td>Details of equipment required</td>
<td>Optional: Precision pipette, tips.</td>
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<tr>
<td><strong>Number of steps to completion of test:</strong></td>
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<tr>
<td>Number</td>
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<td><strong>Endpoint stability:</strong></td>
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<tr>
<td>Time</td>
<td></td>
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<tr>
<td><strong>Time from start to completion:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Time</td>
<td>___ min</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Recommended maximum tests per run:</strong></td>
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<tr>
<td>Test maximum</td>
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<td></td>
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<tr>
<td><strong>Actual number of tests possible per run:</strong></td>
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<tr>
<td>Test number</td>
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<td></td>
<td></td>
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<tr>
<td><strong>Other comments:</strong></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Rating key: 1 = poor; 2 = needs improvement; 3 = satisfactory; 4 = good; 5 = excellent

### 8. Quality control and interpretation of test results

#### 8.1. Test kit controls

If available, manufacturer-supplied positive and negative test kit controls will be run as indicated in the IFU at the commencement of each testing session for RDTs. Where positive and negative test kit controls are not supplied by the manufacturer, as will be the case for many rapid diagnostic tests, external quality control specimens (cholera positive and negative specimens) will act as the control specimens, see later section 9.3.

#### 8.2. Internal control lines for rapid diagnostic tests

Generally, rapid diagnostic tests contain a control band, line or spot to determine that the test device is operating correctly. Most control bands, lines or spots will become visible with the addition of reagent (i.e. buffer) only. However, some rapid diagnostic tests contain a control band, line or spot that becomes visible with the addition of the specimen (i.e. addition of stool specimen). It is imperative that the exact nature of the control band, line or spot is ascertained and recorded in the report. A test run is performed to verify this point before the evaluation starts, if not explicitly mentioned in the IFU.
8.3. External quality control specimen
The WHO Prequalification Evaluating Laboratory supplies an external quality control (QC) specimen which is tested singly at the beginning of each test session for RDTs. The QC specimen represents a weakly reactive specimen, and thus may be different for different assays and different assay formats.

8.4. Proficiency panels
A proficiency panel (V. cholerae) must be run successfully for each assay by each operator before the evaluation commences (this is usually done after the manufacturer training if necessary).

8.5. Limits of acceptability
All results of test kits controls and QC specimens will be entered into the data collection sheets. Should the test kit controls or the QC specimen not give results within the expected ranges, the evaluation process of that assay will be suspended until the cause has been identified and a satisfactory solution is identified. Such problems must be communicated immediately to WHO and must be recorded on the data sheets. The PI will be responsible for carefully checking all data entry forms for legibility, accuracy and completeness.

8.6. Interpretation of results
The interpretation of results for each assay under evaluation will be made strictly according to the manufacturers’ instructions in the IFU. Invalid test results will be recorded in the data collection sheets including where the control line does not appear or in any other way the test result is invalid as defined by the IFU.

9. Analysis of data

9.1. Invalid test devices
Invalid results must be defined according to the manufacturer’s instructions, and may include where the control line, band or spot does not appear, the test is invalid due to an obviously defective test device or to a defective transfer pipette. Specimens that do not flow along or through the membrane will also be considered as invalid results. The number of invalid devices is recorded as the number of invalid test results as a percentage of the total number of devices used for the evaluation.

9.2. Inter-reader variability
Inter-reader variability is calculated when assay readings is performed without objective reading instruments i.e. RDTs. Three persons independently interpret each test result. The inter-reader variability is expressed as the percentage of specimen for which initial test results are differently interpreted (i.e. reactive or non-reactive) by the independent readers.

9.3. Performance characteristics from WHO specimen testing panel
The following approaches will be used to calculate the performance characteristics for each assay under evaluation, and is linked to the reference testing results gained after characterization of all stool specimen included in the performance evaluation.
### Table 4. 2 x 2 table for calculation of performance characteristics

<table>
<thead>
<tr>
<th>Results of assay under evaluation</th>
<th>Results of reference testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>True positives</strong></td>
<td><strong>a</strong></td>
</tr>
<tr>
<td>b</td>
<td>False positives</td>
</tr>
<tr>
<td>Total</td>
<td>a+b</td>
</tr>
<tr>
<td>-</td>
<td>c</td>
</tr>
<tr>
<td><strong>False negatives</strong></td>
<td><strong>d</strong></td>
</tr>
<tr>
<td><strong>True negatives</strong></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
</tr>
<tr>
<td>b+d</td>
<td>a + b + c + d</td>
</tr>
</tbody>
</table>

#### 9.3.1. Sensitivity

Sensitivity is the ability of the assay under evaluation to detect correctly specimens that contain cholera antigen (reference results positive).

Thus sensitivity is the number of true positive specimens identified by the assay under evaluation as positive (a), divided by the number of specimens identified by the reference assays as positive (a+c), expressed as a percentage.

Sensitivity = \( \frac{a}{a + c} \)

#### 9.3.2. Specificity

Specificity is the ability of the assay under evaluation to detect correctly specimens that do not contain cholera antigen (reference results negative). Thus specificity is the number of true negative specimens identified by the assay under evaluation as negative (d), divided by the number of specimens identified by the reference assays as negative (b+d), expressed as a percentage.

Specificity = \( \frac{d}{b + d} \)

#### 9.3.3. Confidence intervals

The 95% confidence intervals will be calculated for both sensitivity and specificity in order to assess the level of uncertainty introduced by sample size, etc. Exact 95% confidence intervals for binomial proportions will be calculated from the F-distribution. [Armitage, 2002; Kirkwood, 2003]

#### 9.3.4. Positive predictive value (PPV)

The probability that when the test is reactive that the specimen does contain cholera antigen. PPVs will be calculated using the formula.

\[
PPV = \frac{(prevalence)sensitivity}{(prevalence)sensitivity + (1 - prevalence)(1 - specificity)}
\]

#### 9.3.5. Negative predictive value (NPV)

The probability that when the test is negative that a specimen does not contain cholera antigen. NPVs will be calculated using the formula.
NPV = \frac{(1 - \text{prevalence})(\text{specificity})}{(1 - \text{prevalence})(\text{specificity}) + (\text{prevalence})(1 - \text{sensitivity})}

The probability that a test result will accurately determine the true infection status of a person being tested varies with the prevalence of cholera infection in the population from which the person comes. In general, the higher the prevalence of cholera infection in the population, the greater the probability that a person testing positive is truly infected (i.e., the greater the positive predictive value [PPV]). Thus, with increasing prevalence, the proportion of individuals testing false-positive decreases; conversely, the likelihood that a person whose test result is negative is truly uninfected (i.e., the negative predictive value [NPV]), decreases as prevalence increases. Therefore, as prevalence increases, so does the proportion of individuals testing false-negative.

The PPV and NPV will be calculated at a prevalence of 0.1%, 1% and 5%.

9.4. Discrepant results
Those specimens with results that are consistent with the reference assays results i.e. the characterized specimen results, undergo no further testing. Those specimens with results discrepant from the reference result are retested in duplicate using the same lot number by the same operator. The results that occur two out of three times are recorded as the test result. If the result is again discrepant, the specimen is retested on a second lot number, if available. If the result on the second lot is concordant with the reference result, no further testing is required. If the result is still discrepant from the reference results, the result is recorded as is.

9.5. Technician's appraisal
The technical aspects of the assay under evaluation will be assessed by the technician who performed the testing. These assessments, along with other selected assay characteristics, contribute to an overall appraisal of each assay’s suitability for use in small laboratories (see Table 3 above).

The data analysis and drafting of the performance report using specified report template is carried out by WHO Performance Evaluating Laboratory and sent to WHO in a timely manner. WHO verifies the draft report and sends it to the authorized contact designated by the manufacturer for comments. The company has a one month period by right to provide comments to WHO. The final report is prepared after one month has elapsed. The WHO scientist ensures that the comments of the authorized contact will be reviewed and any outstanding issues will be resolved before final performance evaluation report is finalized. The final report is prepared and disseminated by WHO. A copy of the final report is sent to the authorized contact designated by the manufacturer.

10. Materials and supplies

10.1. Data collection sheets
All data will be reported to WHO/PQ-diagnostics on the following forms:

A. Data collection Microsoft Excel spreadsheet for the RDTs
   - SO_PDx_311_ Results Template Cholera
B. Technician’s appraisal worksheet
10.2. Supplies
The manufacturers of products will provide the products and any equipment necessary for the evaluation free of charge. WHO will cover the cost of reference testing.

11. Roles and responsibilities

11.1. Responsibilities of the WHO evaluating Laboratory
   a. Conducting the laboratory evaluation in accordance with internationally recognized best practice;
   b. Preparation of QC specimens and proficiency panels;
   c. Preparation of the draft report on the laboratory evaluation;
   d. Advising WHO on operational characteristics of the assays evaluated.

   All source data, data analysis records and all correspondence will be retained and archived for a period of at least ten years.

11.2. Responsibilities of WHO
   a. Technical advice to the PI;
   b. Technical and administrative management of the laboratory evaluation;
   c. Procurement and delivery of supplies and assays required for reference testing;
   d. Verification of the draft report, seeking of comments from manufacturer;
   e. Preparation and dissemination of the final report;
   f. Formal contacts with authorized contacts of the manufacturers.

   Any publication by WHO of the results of these evaluations and the WHO recommendations derived therefrom will, however, be accompanied by the following disclaimer:

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

   WHO and the WHO evaluating Laboratory do not warrant or represent that the performance evaluations conducted with the V. cholera kits referred to in this document are accurate, complete and/or error-free. WHO and the WHO evaluating Laboratory disclaim all responsibility for any use made of the data contained herein, and shall not be liable for any damages incurred as a result of its use. This document must not be used in conjunction with literature used for commercial or promotional purposes.

12. References


International Standards
EN 13612:2002 Performance evaluation of in vitro diagnostic medical devices
ISO 17025:2005 (General requirements for the competence of testing and calibration laboratories)
ISO 15189:2012 (Medical laboratories — Particular requirements for quality and competence)
13. Other documents required

**Evaluation Protocols**
SOP_PQDx_305 Protocol for laboratory evaluation of cholera Rapid Diagnostic Tests

**Work Instructions**
SOP_PQDx_072 PQT work instruction for laboratory testing at WHO Collaborating Centre
SOP_PQDx_074 PQT work instruction for data entry and analysis
SOP_PQDx_075 PQT work instruction for report preparation and dissemination

**Master Templates**
SOP_PQDx_311PQT Report Template for Cholera simple/rapid assays

**Standard Letters**
SOP_PQDX.xxx WHO standard letter for cholera laboratory evaluation protocol
SOP_PQDx_077 PQT standard letter to request test kits:
SOP_PQDx_081 Standard letter for draft report
SOP_PQDx_083 Standard letter for final report (simple/rapid assays)