WHO Emergency Use Assessment and Listing for Ebola Virus Disease IVDs
PUBLIC REPORT

Product: OraQuick® Ebola Rapid Antigen Test Kit
(Cadaveric Oral fluid and Whole Blood)
EUAL Number: EA 0023-021-00

Abstract

Emergency Use Assessment and Listing of In Vitro Diagnostics Procedure

WHO has developed an Emergency Use Assessment and Listing (EUAL) procedure to expedite the availability of in vitro diagnostics (IVDs) needed in public health emergency situations. This EUAL procedure will generate WHO recommendations in order to provide advice to procurement agencies and Member States on the acceptability of a specific IVD in the context of a public health emergency, based on a minimum set of available quality, safety, and performance data and an agreed plan for further evaluation.

As such, the WHO EUAL procedure for IVDs consists of:

- a desktop review of selected manufacturing and quality management system documentation;
- the review of any existing documentary evidence of safety and performance; and
- a limited performance evaluation of relevant performance characteristics of the product.

OraQuick® Ebola Rapid Antigen Test with product codes 1001-0426 and 1001-0427 manufactured by OraSure Technologies, Inc. was listed as eligible for WHO procurement on 24 March 2016.

Assay Principle: OraQuick® Ebola Rapid Antigen Test Kit is an immunochromatographic single-use immunoassay for the qualitative detection of Ebola virus (EBOV) VP40 antigen.

Intended use: The OraQuick® Ebola Rapid Antigen Test is intended for the following two uses:

Whole Blood: For presumptive detection of Ebola Zaire virus in whole blood specimens from individuals with signs and symptoms of Ebola virus infection in conjunction with epidemiological risk factors (including geographical location with high prevalence of Ebola infection). The results should be confirmed by further testing using an approved Ebola virus nucleic acid test (NAT).

Cadaveric Oral Fluid: For detection of Ebola Zaire virus in cadaveric oral fluid specimens to aid in diagnosing Ebola Zaire virus as the cause of death in order to make informed decisions on safe and dignified burial procedures to prevent transmission of the Ebola Zaire virus in

the community. Where possible, the results should be confirmed by further testing using an approved Ebola virus nucleic acid test (NAT).

Intended user: Professional use only.

Methods: Blood and Cadaveric Oral Fluid should be collected and tested as recommended and specifies in the manufacturer instruction for use (IFU)

There are two configurations of the kits as shown in the table below.

Components of Kit	25 Count Kit 1001-0426	100 Count Kit 1001-0427
Divided Pouch, 25 and 100 Each containing: • Test Device(1) • Absorbent Packet (1) • Developer Solution Vial (1) (each vial contains 1.0 mL of a buffered saline solution with an antimicrobial agent)	25	100
Re-usable Test Stands	25	100
Plastic Micropipettes	30	110
Cadaveric Oral Fluid Package Insert	1	1
Whole Blood Package Insert	1	1
Cadaveric Oral Fluid Quick Reference Guide	1	1
Whole Blood Quick Reference Guide	1	1

Materials required and available as an accessory to the kit

OraQuick® Ebola Rapid Antigen Oral Fluid Test Kit Controls (1001-0425)

- Ebola Positive Control (1 vial, orange cap, 0.25 mL)
- Ebola Negative Control (1 vial, white cap, 0.25 mL)
- Package Insert

OraQuick® Ebola Visual Reference Panel (1001-0428)

- Ebola Limit of Detection (1 device)
- Ebola Low Positive(1 device)
- Ebola Negative(1 device)
- Package Insert

Foil Transfer Pouch (1001-0494)

Materials required but not provided

- Timer or watch capable of timing 30 minutes
- Biohazard waste container

Optional materials not provided with kit

- BD Universal Viral Transport for Viruses, Chlamydia, Mycoplasmasand Ureaplasmas

- Σ-Virocult ® System (MW951S)

Storage temperature: 2 to 30 °C.

Stability:
- Test Devices: 12 months stored at 2-30°C
- Kit Controls: 12 months stored at 2-8°C
- Visual Reference Panel: 5 months stored at 15-30°C

Caveats for use of OraQuick Ebola Rapid Antigen Test

1. Weak positive samples may take longer to develop and can take the entire 30 minutes for a test line to be present. Therefore, all negative test results must be read 30 minutes after inserting the device in the Developer Vial. Negative test results must not be reported prior to reading the device at 30 minutes.
2. Reading any test result after 30 minutes may yield inaccurate test results.
3. Negative results do not preclude Ebola virus infection.
4. Potential cross reactivity of the OraQuick Ebola Rapid Antigen Test with Ebola vaccines and therapeutics has not been evaluated. Individuals (live or deceased) who have received therapeutics or vaccines against Ebolavirus may exhibit false positive or other confounding test results.
5. Cross-Reactivity with organisms related to oral fluid have not been assessed and may lead to erroneous results.

WHO EUAL Assessment

OraSure Technologies, Inc. submitted an expression of interest for WHO emergency quality assessment of **OraQuick Ebola Rapid Antigen Test** kit on **23 March 2015**.

1. Product dossier assessment

OraSure Technologies, Inc. submitted documentation in support of safety and performance for OraQuick Ebola Rapid Antigen Test Kit as per the "Invitation to Manufacturers of Ebola Virus In Vitro Diagnostics to Submit an Expression of Interest (EOI) for Emergency Assessment by WHO".[1] The information submitted in the product application was reviewed by WHO staff and external experts (reviewers) appointed by WHO. The findings of the reviews were reported in accordance with "Emergency Quality Assessment Mechanism of In Vitro Diagnostics for Ebola Virus Protocol for the Review of Documentary Evidence of Safety, Quality and Performance" (document number WHO PQDx_0188 v0.2).

Safety and performance documentation for Emergency Use Assessment and Listing **conclusion: acceptable.**

[1] Invitation to manufacturers of Ebola virus in vitro diagnostics to submit an Expression of Interest (EOI) for emergency assessment by WHO. Accessed on 24 November 2014 at http://www.who.int/diagnostics_laboratory/141002_revised_invitation_to_mx_of_ebola_virus_diagnostics_rc.pdf?ua=1

2. Review of quality management documentation

To establish the eligibility for WHO procurement, OraSure Technologies, Inc. was asked to provide up-to-date information about the status of their quality management system.

Based on the review of the submitted quality management system documentation, it was established that sufficient information was provided by OraSure Technologies, Inc. to fulfil the requirements described in the "Invitation to manufacturers of Ebola Virus In Vitro Diagnostics to submit an Expression of Interest (EOI) for emergency assessment by WHO".

Quality management documentation for Emergency Use Assessment and Listing c**onclusion: acceptable.**

3. Laboratory evaluation (cadaveric oral fluid)

OraQuick Ebola Rapid Antigen Test Kit was evaluated independently by WHO-supported European Union and African Union field laboratories at Kambia, (Sierra Leone) using 51 archived Ebola positive and 193 Ebola negative archived oral fluid specimens. The RDT was read by two blinded readers, with a third blinded reader used in cases of discrepancy between the first two readers. Out of 244 specimens tested 2 (0.8%) were discrepant between readers. The performance of the OraQuick Ebola Rapid Antigen Test assay is shown in the table below

	Xpert Ebola Test (Cepheid)	
	Positive	**Negative**
	Number **Sensitivity** **(95% CI)**	**Number** **Specificity** **(95% CI)**
OraQuick Ebola Rapid Ag Test (Orasure)	48/51* 94.12**%** (83.76-98.77)	193/193 100.00**%** (98.11-100)

*Seventeen (17) out of the fifty-one (51) samples were dilutional samples. Two of the three positive results that were incorrectly interpreted as negative were samples that were diluted.

Limitations of the performance evaluation

One of the main limitations of the study was the use of oral fluid specimens which were collected on devices and stored in transport medium other than those recommended by the various manufacturers. Also the use of aged rather than fresh specimens could have affected the performance of the assays.

4. Laboratory evaluation (whole blood)

A total of 75 retrospective, remnant whole blood samples collected from patients in West Africa (Sierra Leone) during the 2014-2015 Ebola outbreak were tested with the OraQuick® Ebola Rapid Antigen Test at the Centers for Diseases Control (USA). These samples were tested in West Africa

using an U.S. FDA Emergency Use authorized (EUA) Ebola Virus Real-time RT-PCR Assay. The whole blood samples were stored frozen thereafter until testing with the OraQuick® Ebola Rapid Antigen Test. Testing was performed in a randomized, blinded manner. OraQuick® Ebola Rapid Antigen Test performance in comparison to the results generated by the EUA Ebola Virus Real-time RT-PCR Assay (the Comparator) were calculated based on OraQuick® Ebola Rapid Antigen Test results that were read at 30 minutes.

Positive and Negative Percent Agreement against the Comparator

	Percent Agreement	**95% CI***
Positive Percent Agreement	84.0% (21/25) [§]	63.92% - 95.46%
Negative Percent Agreement	98.0% (49/50)	89.35% - 99.95%

*Calculated using Clopper-Pearson exact method
§Includes specimens tested in a Ct range 15-34 (Refer to the table containing the Percent Agreement for Select Ct Ranges)

Percent Positive Agreement for select Ct Ranges

PCR Ct Ranges	**Percent Agreement**	**95% CI***
15 – 24	100% (16/16)	86.77% - 100.0%
15 – 29	90.5% (19/21)	69.62% - 98.83%
15 – 34	84.0% (21/25)	63.92% - 95.46%

*Calculated using Clopper-Pearson exact method

Laboratory evaluation for Emergency Use Assessment and Listing conclusion: Acceptable as a screening assay in suspected Ebola virus disease whole blood and cadaveric oral fluid specimens during the current Ebola virus outbreak in West Africa.

WHO Emergency Use Assessment and Listing Decision

Based on the review of the manufacturer's submitted data, as well as data generated from the limited field laboratory evaluations using West African population OraQuick Ebola Rapid Antigen Test Kit and associated controls, are eligible for WHO procurement. Due to the relatively lower sensitivity and specificity of antigen tests compared with RT-PCR, the OraQuick® Ebola Rapid Antigen Test is for the presumptive detection of Ebola Zaire virus disease in individuals with signs and symptoms of Ebola virus infection and in cadaveric oral fluid specimens from deceased individuals to aid in diagnosing Ebola Zaire virus as the cause of death in order to make informed decisions on safe and dignified burial procedures to prevent transmission of the Ebola Zaire virus in the community.. Where possible, the results should be confirmed by testing a new blood sample using an approved Ebola virus nucleic acid test (NAT). A final interpretation of the results should be made in conjunction with epidemiological and patient clinical parameters to make a final clinical judgement.

Ebola-specific safety precautions should be taken when using the rapid test.

Post market surveillance to monitor the performance of OraSure Technologies, Inc. Kit in comparison with supplemental NAT is highly recommended.

Scope and duration of procurement eligibility

OraQuick Ebola Rapid Antigen Test Kit with product codes 1001-0426, 1001-0427, manufactured by OraSure Technologies, Inc. is considered to be eligible for WHO procurement. The assay may be used to test symptomatic individuals for Ebola virus disease. This listing does not infer that the product meets WHO prequalification requirements and does not mean that the product is listed as WHO prequalified.

As part of the on-going requirements for listing as eligible for WHO procurement, OraSure Technologies, Inc. must engage in post-market surveillance activities to ensure that the product continues to meet safety, quality and performance requirements. OraSure Technologies, Inc. is required to notify WHO of any complaints, including adverse events related to the use of the product within 7 days of receipt. Furthermore, WHO will continue to monitor the performance of the assay in the field.

WHO reserves the right to rescind eligibility for WHO procurement, if additional information on the safety, quality and performance comes to WHO's attention during post-market surveillance activities.