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

Product: Xpert Ebola Assay
EUAL Number: EAE 0443-070-00

Abstract

In order to respond to the urgent need for quality-assured in vitro diagnostics in the event of an Ebola Virus Disease (EVD) outbreak, WHO has established a WHO Emergency Quality Assessment Mechanism of In Vitro Diagnostics (IVDs) for EVD. It consists of a review of any existing evidence of safety and performance; desktop review of selected manufacturing and quality management systems documentation and limited laboratory evaluation of the product.

Xpert Ebola Assay with product code **GXEBOLA-10** manufactured by Cepheid AB, Röntgenvägen 5, Solna, 171 54, Sweden was listed as eligible for WHO procurement on 8 May 2015. This public report was amended on 13 June 2019 to reflect the planned inclusion of the latest Instructions for Use.

Assay principle: The Xpert Ebola Assay is a rapid, automated test for qualitative detection of the Zaire strain of the Ebola virus. The assay is performed on the Cepheid GeneXpert Instrument Systems. The GeneXpert Instrument Systems automate and integrate sample purification, nucleic acid amplification, and detection of the target sequence in simple or complex samples using real-time reverse transcription PCR. The systems consist of an instrument, personal computer, and preloaded software for running tests and viewing the results. The systems require the use of single-use disposable GeneXpert cartridges that hold the real-time reverse transcription PCR reagents and host the real-time reverse transcription processes. Because the cartridges are self-contained, cross-contamination between samples is minimized. For a full description of the systems, refer to the appropriate GeneXpert Dx Operator Manual or GeneXpert Infinity Operator Manual.

Intended use: The Xpert Ebola Assay is a real-time reverse transcription polymerase chain reaction (RT-PCR) test intended for the qualitative detection of RNA from the Ebola Zaire virus (detected in the West Africa outbreak in 2014) in EDTA venous whole blood from individuals with signs and symptoms of Ebola virus infection in conjunction with epidemiological risk factors.
Testing with the Xpert Ebola Assay should not be performed unless the individual meets clinical and epidemiological criteria for testing of suspected cases. Results are for the presumptive identification of Ebola Zaire virus. The definitive identification of Ebola Zaire virus infection requires additional testing and confirmation procedures in consultation with public health or other authorities for whom reporting is required.
The diagnosis of Ebola Zaire virus infection must be made based on history, signs, symptoms, exposure likelihood, and other laboratory evidence in addition to the identification of the Ebola Zaire virus. Negative results do not preclude Ebola Zaire or other Ebola virus infections and should not be used as the sole basis for patient management decisions. The level of Ebola

virus present in blood from individuals with early systemic infection is unknown. Due to the difficulty in obtaining clinical specimens positive for Ebola, the Xpert Ebola Assay was evaluated with limited numbers of contrived specimens spiked with live Ebola Zaire virus or Ebola Zaire virus RNA. The assay has not been evaluated with blood from individuals with Ebola Zaire virus infection.

Intended user: Clinical laboratory personnel who have received specific training on the use of the Xpert Ebola Assay on the GeneXpert Instrument Systems.

Limitation: Reactivity of the Cepheid Xpert Ebola Assay was not evaluated with isolates of the *Bundibugyo ebolavirus* and *Sudan ebolavirus* species, instead *in silico* analysis was performed to predict the risk of cross-reactivity of the Xpert Ebola Assay Zaire target oligonucleotides to non-Zaire Ebola viruses. As a result detection of Bundibugyo or Sudan viruses are unlikely but cannot be entirely ruled out.

There is only one configuration of the Xpert Ebola Assay kit which contains sufficient reagents to process 10 specimens or quality control samples.

Component	**Number per kit (GXEBOLA-10)**
GeneXpert Ebola Assay Cartridges with Integrated Reaction Tubes • Bead 1, Bead 2, and Bead 3 (freeze-dried) 1 of each per cartridge • Rinse Reagent 0.5 mL per cartridge • Elution Reagent 2.0 mL per cartridge • Binding Reagent	10 1 of each per cartridge 0.5mL per cartridge 2.0mL per cartridge 2.0mL per cartridge
Ebola Sample Reagent Bag (Sample Reagent) • Lysis Reagent (Guanidinium Thiocyanate)	1 10 x 2.5mL per bottle
Disposable 1 mL Transfer Pipettes	10
CD	1
Instructions for use	1

Materials Required but Not Provided

Material	**Catalogue number**	**Description**
GeneXpert Dx System or GeneXpert Infinity Systems	varies by configuration	GeneXpert Instrument, computer with proprietary GeneXpert Software Version 4.4a or higher, Xpertise 6.2 or higher, barcode scanner, and operator manual
Printer (optional)	NA	Contact Cepheid Technical support to arrange for the purchase of a recommended printer.
Disposable Swabs	# SWAB/E-50	
Vortex	NA	
Chlorine Bleach	NA	

Stability

Name	Storage temperature	Shelf-life
GeneXpert Ebola Assay Cartridges	2 – 28 °C	12 months
Ebola Sample Reagent Bag (Sample Reagent)	2 – 28 °C	12 months

Background information

Cepheid AB submitted an expression of interest for WHO emergency quality assessment of **Xpert Ebola Assay** on 20 October 2014.

1. Product dossier assessment

Cepheid AB was granted Emergency Use Authorization by the U.S Food and Drug Administration for the **Xpert Ebola Assay** in March 2015. The information submitted to FDA and the outcome of the review was considered sufficient to fulfil requirements for eligibility for procurement by WHO.

Safety and performance documentation assessment conclusion: acceptable.

2. Review of quality management documentation

To establish the eligibility for WHO procurement, Cepheid AB 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 Cepheid AB 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 assessment conclusion: acceptable.

3. Laboratory evaluation

A limited analytical evaluation of the **Xpert Ebola Assay** was conducted by the Bernhard Nocht Institute for Tropical Medicine (BNITM) in Hamburg, Germany which is a WHO Collaborating Centre for Arbovirus and Haemorrhagic Fever Reference and Research. The limit of detection (LOD) of the assay was verified and compared to the RealStar Filovirus Screen RT-PCR Kit 1.0 (altona Diagnostics GmbH) using simulated specimens generated by spiking cell culture supernatants containing infectious Ebola virus strain Makona into whole blood of a healthy donor. The evaluation of the **Xpert Ebola Assay** was performed on the GeneXpert-IV System.

The 95% limit of detection of the assay was found to be 82.0 RNA copies/reaction, 95% CI 39.7 to 3193.6 copies/reaction.

Laboratory evaluation conclusion: acceptable.

Commitment to WHO

As a requirement to listing, the manufacturer is required update the current version (Rev. C January 2019) of the instructions for use by 31 July 2019.

Scope and duration of procurement eligibility

The **Xpert Ebola Assay** with product code GXEBOLA-10 manufactured by Cepheid AB is considered to be eligible for WHO procurement. The assay may be used to test symptomatic individuals for EVD. 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, Cepheid AB must engage in post-market surveillance activities to ensure that the product continues to meet safety, quality and performance requirements. Cepheid AB is required to notify WHO of any complaints, including adverse events related to the use of the product within 7 days. 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.

Note that the CE-marked version of the product **Xpert Ebola Assay** with product codes GXEBOLA-CE-10 and GXEBOLA-CE-50 has not been listed through the EUAL Procedure for IVDs, as the instructions for use for the CE marked version of the product are not in agreement with the WHO interim guideline "Laboratory diagnosis of Ebola virus disease".[1]

[1] https://apps.who.int/iris/bitstream/handle/10665/134009/WHO_EVD_GUIDANCE_LAB_14.1_eng.pdf;jsessionid=A3DE1D81428B145F3277633657239395?sequence=1

Labels

1.0 Instrsutctions for Use