EUROPEAN COMMISSION

View in the context of the context of the Performance Evaluation Consultation Procedure (PECP)

Expert panels on medical devices and in vitro diagnostic devices (Expamed)

Contents

Scope of this expert view

This scientific view reflects the opinion of independent experts (MDR Article 106.1) on the performance evaluation report (PER) of the manufacturer. The advice is provided in the context of the performance evaluation consultation procedure (PECP), which is an additional element of conformity assessment by notified bodies for specific high-risk in vitro diagnostic devices (IVDR Article 48.6).

When making its conformity assessment decision, the notified body is obliged to give due consideration to the opinions expressed in the scientific view of the expert panel, where applicable (Annex IX, Section 4.9 or, as applicable, Annex X, Section 3, point (j)).

For class D devices, the notified body must provide a full justification in the case of divergent views between the notified body and the experts. This justification shall be included in the notification to the competent authority (IVDR Article 50; mechanism for scrutiny of class D devices).

1 ADMINISTRATIVE INFORMATION

Date of reception of the dossier	07/07/2022
Notified Body number	2797
Internal PECP dossier #	IVD-2022-000016
***In vitro* diagnostic medical device**	Real-time reverse transcription polymerase chain reaction (RT-PCR) test for the qualitative detection of Zaire Ebola virus' RNA in EDTA venous whole blood or peripheral blood in adults.

2 INFORMATION PROVIDED BY THE NOTIFIED BODY

When consulting the IVD expert panel, the notified body provided the below information on the type of device in accordance with MDCG 2021-22.

Intended purpose (P)		
P1	what is detected and/or measured *please specify the analyte(s) or marker(s), e.g. SARS-CoV-2 spike protein, Kel1 (K)*	Glycoprotein (GP) gene and/or nucleoprotein (NP) gene
P2	function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc*	Aid to diagnosis
P3	the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate *e.g. hepatitis C infection, exposure to SARS-CoV-2, risk of HIV transmission in blood transfusion etc.*	Identification of Ebola Zaire virus
P4	whether it is automated or not	Automated
P5	whether it is qualitative, semi-quantitative or quantitative	Qualitative
P6	type of specimen(s) *e.g. whole blood, serum, saliva etc*	EDTA venous whole blood or peripheral blood from finger-stick

P7	where applicable, the testing population *e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range*	Adults with signs and symptoms of Ebola Virus Disease (EVD) in conjunction with epidemiological risk factors
P8	intended user	Trained users in a laboratory setting
Technology (T)		
T1	principle of the assay method or principles of operation of the instrument *e.g. real-time PCR, qualitative PCR, digital PCR, sandwich immunoassay, competitive immunoassay, immunoturbidimetric assay etc.*	Reverse transcriptase real-time PCR

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group

Date of views	05/09/2022
Expert panel name	IVD expert panel
Sub-group of expert panel (where relevant)	IVD sub-group 2022-16

3.2 Summary of expert panel views

So far Common Specifications for Ebola virus (EBOV) screening tests are not yet defined.

The test is an *in vitro* nucleic acid test (NAT) for the qualitative detection of Zaire EBOV RNA in EDTA venous whole blood or peripheral blood from finger-stick of adults with signs and symptoms of Ebola Virus Disease (EVD) and in conjunction with epidemiological risk factors. The Zaire EBOV was detected in the West Africa outbreak between 2013 and 2016. Given the potential risks of false negative results, the assay should not be used unless the individual meets clinical and epidemiological criteria for testing of suspected cases. Negative results do not preclude Zaire EBOV or other EBOV infections and should not be used as the sole basis for patient management decisions. Confirmatory testing at the public health laboratory is necessary for positive detection results and may be necessary for negative detection results.

The assay is intended for use on a prespecified system. The instrument system (platform) used, is also used for the diagnostics of several other virus infections. The instrument system

automates and integrates sample preparation, nucleic acid amplification, and detection of the target sequence in simple or complex samples using real-time reverse transcription PCR (RT-PCR). The platform consists of an instrument, personal computer, barcode scanner, and preloaded software for running tests and viewing the results.

The test includes reagents for the detection of Zaire EBOV total nucleic acids in specimens as well as a sample adequacy control and an internal control to ensure adequate addition of the sample, processing of the target and to monitor the potential presence of inhibitor(s) in the reverse transcription and PCR reactions. Reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability is verified by a control system.
The Operator Manual describes intended use, non-clinical and clinical performance evaluation. Procedures and limitations are described, including the potential of mutations affecting performance. The system requires the use of single-use disposable 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.

The instructions for use (IFU) describe the intended use, detailed description of procedures, non-clinical and clinical performance evaluation. It was noted that the IFU text in the PER was not identical to the text in the separate file, as the text in the PER still included the possibility of a buccal swab. The more current document was used for this assessment, such mix-up of different versions should be avoided. The claimed limit of detection (LoD) for Ebola Zaire Mayinga RNA in EDTA-WB is determined to be 232.4 copies/mL (95%CI: 63.1-301.6) and the LoD for Ebola Zaire Makona-Gueckedou virus in EDTA-WB is determined to be 1.0 PFU/mL.

Analytical reactivity (inclusivity) for the test is 100% for the Ebola Zaire strains Guinea, Ekron, Gabon, and Kikwit. *In silico* analysis results indicate that the device appropriately identifies all the Ebola Zaire sequences in GenBank.

Analytical specificity of the test is 100%. No cross-reactivity with several other microorganisms was found.

The World Health Organization endorsed two International Reference Preparations (IRP) for NAT assays designed to detect Zaire EBOV RNA. These two non-infectious synthetic IRP (EBOV RNA NP-VP35-GP, EBOV RNA VP40-L; distributed by NIBSC, UK) are based on lentivirus vectors with integrated Zaire EBOV sequences, covering together the whole EBOV genome. Based on the international collaborative study results obtained by a variety of different assays an unitage has been assigned to these IRP. Though the IRP have not been assigned the status of International Standards (IS), the preparations are estimated as well-characterized reference materials with comparative data obtained by a variety of further NAT assays. It is strongly advised to include these IRP for further comparative characterization of analytical sensitivity of the test under question.

Although this presentation shows high analytical sensitivity and specificity, it lacks sufficient insight into clinical diagnostic accuracy of the test, where mock specimens were used as proxy

for clinical specimens. The approach chosen is relevant but does not represent different and specific conditions, including dynamic infection pressure and different clinical presentations. It appears critical to correctly confirm or reject the possible diagnosis for both optimal patient management and epidemic control into account. This is reflected in the described test limitations. However, the absence of clinical data is important. It is recommended that the manufacturer presents more data on true clinical samples according to sensitivity, specificity, positive predictive value (PPV) and negative predicted value (NPV) including 95% confidence interval, given the importance of accurate estimation of sensitivity, specificity, PPV and NPV for adequate patient care in relation to infection pressure. Within the scope of the IVDR, a post-market clinical study as part of the required postmarket surveillance should be considered as soon as a respective outbreak may occur.

As within the scope of IVDR the test is intended for use in the EU and EU populations, it is noted that there is no discussion on this subject in the PER. This is particularly relevant in relation to the intended use described in the IFU.

A comprehensive literature review focusses on different aspects of the test performance of the platform.

Regarding the dossier the expert views were generally in line with each other. The overall opinion on the content of the dossier was positive, although there were some general and specific issues noted by the experts that were insufficiently addressed or not at all by the manufacturer. Recommendations from these observations are listed under 3.5.

The following observations were noted by the experts:

Overall analytical sensitivity and specificity are high and appear promising for the intended purpose of this diagnostic assay. The characterization of assay sensitivity using the well-characterized WHO IRP is still missing.

Clinical performance of the test was conducted on contrived samples due to the limitation of clinical specimens available for the EBOV diseased patient material. This limits the assessment of actual clinical performance of the test in the epidemic situation and the clinical presentation of the patients. It is important that efforts are made to obtain more clinically relevant samples as an accurate insight into the performance of the test. Respective data are crucial for actual routine patient management and epidemic control.

At low background incidence the risk of false positivity increases. In outbreak settings a false negative test may have serious consequences. For that reason, the IFU mentions that all positive and negative test should be confirmed. If not observed in clinical studies, specimen from clinical patient data should come from post-market experience. A post-market risk management report including a residual risk assessment and a limited Periodic Safety Update Report (PSUR) covering only a period between 2020-2021 is included. The manufacturer appears to not recognize the need for a Post-Market Performance Follow-up (PMPF). This estimation should be reconsidered since active post-market follow-up is essential to assure

the safe use and the benefits and risks of implementing the test, especially in low or unpredictable incidence settings.

In summary, in the current situation with fortunate absence of EBOV outbreaks (and respective clinical samples) the experts were positive about the content and extent of the submitted dossier. However, some recommendations for improvement of the assay evaluation are summarized in section 3.5.

3.3 Views on the specific reports included in the performance evaluation report (PER)

(IVDR, Annex XIII, Section 1.3.2, first paragraph)

Views of the expert panel on the performance evaluation report of the manufacturer (PER)
1. Expert views on the scientific validity report[1]
Scientific validity report gives a comprehensive summary of scientific literature, comparison to one other device measuring the same analyte/marker, consensus expert opinions/guidelines, and results from other sources of clinical performance. Twenty-two peer-reviewed articles issued between 1996 and 2020 were considered for the analysis of the best diagnostic strategy detecting the Zaire EBOV from whole blood. Seventeen peer-reviewed publications of studies on EBOV target sequences mainly located in the NP (33.3%), GP (21.0%), and L (38.6%) regions of the EBOV genome, comprising 57 primers in the oligonucleotide database. Based on this review the test has been developed as a real time reverse-transcription PCR including primers and probes targeting highly conserved sequences in the GP and NP genes of Zaire EBOV for detection of Zaire EBOV species from whole blood and peripheral blood from fingerstick. The scientific validity of GP and NP genes and their association with detection of Zaire EBOV has been established. The experts agree that the measurement of this analyte in biological specimens from patients infected by EBOV is considered scientifically valid and is consistent with the current state of the art (SOA).
2. Expert views on the analytical performance report[2]
The analytical performance report (APR) gives a short overview of the analytical performance studies with reference to IVDR requirements. The procedures to establish analytical

[1] Annex XIII, Section 1.2.1 of Regulation (EU) 2017/746 - Demonstration of the scientific validity
[2] Annex XIII, Section 1.2.2 of Regulation (EU) 2017/746 - Demonstration of the analytical performance

performance is described in detail in the analytical performance plan. The APR provides a systematic overview of all the steps taken to ascertain the technical performance of the assay. For more details (e.g., objectives, preparation of test panels, testing procedures and results) reference is made in the three individual studies from Sweden, Canada, and Texas. This precludes an efficient evaluation of the tests performed and validity of the methods and results. The summary report describes the technical performance verifications, assay specific analysis package development and verification design transfer activities, and stability studies.

The technical performance verifications (TPVs) included various parameters: limit of detection, precision (repeatability within laboratory, reproducibility), verification of different genotypes, dilutional sensitivity, diagnostic specificity, interference (endogenous and exogenous), specimen type (matrix equivalency) and stability, analytical sensitivity and reactivity, assessment of carry-over contamination, sample hold time, external control evaluation, evaluation of virucidal efficacy, time to result, clinical specimen stability, lot interchangeability.

The manufacturer's analytical performance report provides data for demonstration of the analytical performance of the device in relation to all parameters of the analytical performance. Data are available for making decisions if the assay is appropriate for use from analytical point of view. Analytical performance is well conducted for EBOV Zaire Mayinga (LoD for Ebola Zaire Mayinga and Ebola Makona-Gueckedou). The manufacturer demonstrated the analytical performance of the device in relation to specimen type with the following performance parameters specificity, sensitivity, absence of interference and cross-reactivity, interchangeability stability. The results are in agreement with the descriptions in the IFU. It is strongly recommended to complement analytical characterization of the assay with inclusion of the WHO IRP for Zaire EBOV RNA.

There is no head-to-head comparison with other NATs. The absence of such comparisons is not discussed. Analytic sensitivity was studied for four Zaire Ebola strains, Guinea, Ekron, Gabon (all live virus), Kikwit (RNA) and was 100%.

To establish analytic specificity a large number of pathogens was tested, including other haemorrhagic fever viruses, and pathogens (viruses, bacteria, parasites) known to co-circulate in the epidemic region(s). This also included the following non-Zaire Ebola strains: Ivory Coast & Reston (RNA), Sudan-Boniface, Sudan-Bunidbugyo, Sudan-Gulu (RNA). So, analytical specificity of the test is 100%. No cross-reactivity with several other microorganisms was found, except against samples containing Marburg virus Ravn and Musoke (RNA). Further analysis and experiments (e.g. sequence analysis of the amplicons, testing of live virus) concluded that the initial results have been due to contamination of the samples with Zaire EBOV RNA.

The absence of assay calibration, linearity, limit of quantification, trueness and accuracy is justified by stating that the test is qualitative.

Regarding the unavailability of real clinical specimens from EBOV infected patients the manufacturer has evaluated the test using contrived EDTA whole blood specimens with EBOV Zaire Mayinga and cultured viral EBOV Makona-Gueckedou. The acceptability of this approach is also discussed in the clinical performance report.

Stability study as sample hold time, supports stability in a controlled setting up to 5 hours and 35°C.

Some observations were noted by the reviewers and are, if applicable included in the recommendations. These observations include:

- Information on the detection limit regarding plaque forming units (PFU) is misleading and should be presented with caution. Since the assay detects the viral genome irrespectively of the infectivity of the virus, the information of LoD of 1.0 PFU/ml applies only for this testing arrangement and might be different in real patient samples. If described as such in the IFU, this should be clarified.
- Stability study as sample hold time between sample addition and cartridge processing, supports stability in a controlled setting up to 5 hours and 35°C. This may not reflect actual day-to-day practice in the geographic setting and should be reflected on.
- Missing comparison with other EBOV NAT methods. The literature search, however, identified and appraised articles evaluating the performance of the test supporting its intended use. The findings presented in these papers demonstrated that the performance of the test evaluated with established comparators and/or equivalent products is comparable to the results of the clinical performance study.

Residual risks, limitations, precautions, and cautions are adequately captured in the product labelling. The assessment of the clinical evidence demonstrated the safety and performance of the test when used as intended in accordance with the product labelling, but only for mock clinical specimens. There are two residual risks addressed in the Risk Management Plan. But absence of clinical performance data from clinical patient specimens and the suitability of use of the test in the EU setting should be added.

3. Expert views on the clinical performance report[3]

The clinical performance consisted of the scientific validity report (see above), clinical validation plan and clinical performance report.

[3] Annex XIII, Section 1.2.3 of Regulation (EU) 2017/746 - Demonstration of the clinical performance

The clinical validation plan refers to the same TPVs as included in the analytical peformance report.

The clinical performance report mentions that no clinical performance studies with real patient samples are conducted under IVDR. One clinical study was conducted using contrived clinical samples, but the test has not been evaluated with blood from individuals with Zaire EBOV virus infection, as it should be in a comprehensive study.

The parameters evaluated in the study include positive percent agreement and negative percent agreement. Likelihood ratio, expected values, PPV and NPV in normal and affected populations have not been evaluated as these parameters are not applicable to the specimens used as they were all contrived.

Reproducibility was evaluated for GP and NP targets by four repeats and for separate GP and NP targets by five repeats. The reproducibility was also checked with a study conducted in three different sites and operators with 144 negative, 144 low and 144 moderate positive samples, and the results demonstrated acceptable reproducibility and precision performance.

The analytical sensitivity was tested with 4 different concentrations (1xLoD – 100xLoD) of well-characterized diluted standards of the target viruses. The results are discussed in the clinical performance report. Reference is made to the report of the retrospective study. These two clinical studies used spiked samples only. The manufacturer has evaluated the diagnostic sensitivity of the assay in known positive samples, as is expected in a comprehensive clinical performance report.

The clinical performance report mentioned historical data of approximately 200,000 performed test during the recent Ebola outbreak in 2018/2019 , mainly through WHO procurement. But the information of the post-market analysis is based mainly on the internet search.

Some observations were noted by the reviewers and are, if applicable, discussed in the recommendations. These include:

- Clinical specimens were not available due to difficulties and safety risks obtaining them at time of the clinical study in 2015. During the Ebola outbreak in 2018/2019 when there was extensive use of the test, no specific post-market data collection or clinical study in real-life setting was performed. Correct diagnostic procedures are critical in these patients for patient management and epidemic control.
- The negative percent agreement (NPA) acceptance criterion is ≥99% with a lower limit of ≥88%. Given the consequences of false negative outcomes, a further justification of the acceptability of this lower limit could be considered, especially in absence of true clinical specimens data.

3.4 Views on specific assessment aspects of the performance evaluation report (PER)

(IVDR, Annex XIII, Section 1.3.2, second paragraph)

Views of the expert panel on the specific aspects included in the performance evaluation report of the manufacturer (PER)
1. The justification for the approach taken to gather the clinical evidence
This device is intended for diagnosis of all known strains of Zaire EBOV in EDTA venous whole blood or peripheral blood from finger-stick from individuals with signs and symptoms of EVD in conjunction with epidemiological risk factors. Clinical performance data was gathered from three different laboratories but based on contrived samples only. This approach was taken because of the reported difficulties and risk of obtaining true clinical samples. It is not clarified why during the 2018/2019 outbreak, no study using true clinical samples was conducted despite the widespread use of the test. The experts` view is that overall clinical evidence for the intended use of the device to support safety and intended clinical benefits is partly sufficient. Indeed, performance of the test in clinical specimens under different and specific conditions, including dynamic infection pressure and different clinical presentations, is critical to correctly confirm or reject the possible diagnosis for both optimal patient management and epidemic control. The absence of actual post-market surveillance from the Ebola outbreak is not justified. Within the scope and obligations of the IVDR, a post-market clinical performance study to address the noted missing information should be considered. It should be noted that the applicability of this test in an EU population, which is the purpose of this assessment, is not discussed. Issues for consideration were expressed by the expert panel as addressed in section 3.2.
2. The literature search methodology, protocol, and report
The literature search covering the period 2014-2021 described guidance documents for appropriate EBOV testing under Emergency Use from WHO, FDA, CDC. The literature review of the peer-reviewed scientific literature result in three articles issued between 2017-2020 focusing on the continuous monitoring of mutations associated with the nucleoprotein (NP) and/or glycoprotein (GP) Ebola gene targets will be an on-going PMPF process to ensure that the test remains the SOA. For the intended purpose of the assay, the review on scientific validity is adequate. A brief description comparing the test with five other products on the market regarding assay sensitivity were presented. However, a laboratory comparison of these assays with the spiked samples used for the test evaluation is missing. Post-market data collected and evaluated during the reporting period (01.02.2020 – 31.07.2021) based on an internet search by PubMed, Science Direct and Google Scholar, did

not identify any significant finding that would need to be addressed through additional risk mitigation or management activities. The data indicated that the IFU and analysis reports are consistent. Post-market data has shown that the test is still considered SOA.

3. The technology on which the device is based, the intended purpose of the device and any claims made about the device's performance or safety

The appropriateness of the technology to reach the intended purpose of the device and the manufacturer's claims regarding performance and safety of the device is in agreement with the IVDR. Innovative aspect is moderate because the company combined this assay with another diagnostic assay already in use.

The technology used, a nucleic acid test (NAT) for EDTA venous blood samples from patients represents a qualitative molecular method using EBOV RNA target amplification by real-time PCR amplification and detection.

The technology on which the device is based as well as the intended purpose of the device are detailed in the dossier.
The test is based on real-time PCR technology: nucleic acid extraction and purification followed by PCR amplification and detection. Viral nucleic acids from the patient blood samples are released by proteinase and lysis reagent, and impurities are removed. Primers selected from highly conserved regions of the viral nucleic acid provide a selective amplification of target viruses from the sample. Specific Zaire EBOV detection probes for the virus nucleoprotein (NP) gene and the glycoprotein (GP) gene using are labelled with one of ten unique fluorescent dyes, which are measured at defined wavelengths, thus permitting simultaneous detection and discrimination of the amplified two targets and Internal Control.
The use of nucleic acid test (NAT) technology is fit for purpose.
Also, the manufacturer targeted this assay for the NP and GP regions of the Zaire EBOV strain, and this renders the assay ineffective for universal detection of other filoviruses like EBOV Ivory coast, EBOV Reston, Lassa virus or Marburg virus. Regarding the specificity, this assay benefits of a double targeting in the genomic sequence of NP and GP of the Zaire EBOV.

Nucleic acid test technology has been used in diagnosis of acute virus infections to decrease the "diagnostic window" between initial infection and the detection of specific antibodies. These assays are also widely used for diagnosis of other infectious agents. The use of the current technology under assessment limits the risk of contamination and is fit for purpose. Performance of safety of the device is addressed. Claims should be covered in the IFU.

The Risk Management Report contains the summary of the device risk and safety and the justification that the overall benefits outweigh the risks. There has been a risk assessment performed and each of the individual risk's levels has been justified as acceptable and within the comparable SOA technologies. The benefits of the product justify the overall residual risk

acceptability. There have been no performance or safety concerns reported so far in the post-market period. There are no residual risks to be addressed by additional post-market studies.

4. Acceptability of clinical evidence (clinical data and performance evaluation results) against state of the art in medicine

Clinical evidence is presented in the analytical performance report, the scientific validity report, and the clinical performance report. The dataset is extensive and sufficient to assure analytical precision. Particularly the analytical dataset has provided extensive information on sensitivity, specificity, reproducibility, and stability. The manufacturer has performed one clinical performance study, but only in contrived samples. No other sources of evidence were provided.

The experts consider that the assay is a SOA product considering some factors:

First, the clinical performance report justifies the absence of clinical specimens due to difficulties and safety risks obtaining them at time of the clinical study. During the Ebola outbreak in 2018/2019 when there was extensive use of the test, no specific postmarket data collection or clinical study in real life setting was performed. Correct diagnostic procedures are critical in these patients both for patient management and epidemic control.

Secondly, the assay complies with the general safety and performance requirements.

Besides, the manufacturer has addressed the performance of the product in comparison to other devices measuring the same analyte/marker by using published scientific literature.

Finally, the Scientific Validity Report describes the SOA determination for the detection of EBOV in whole blood or finger-prick samples and establishes that the device qualifies as SOA in medicine.

In summary, the clinical evidence provided by the manufacturer is estimated sufficient to determine suitability of the assay to safely be utilised for the intended use its intended use in individuals with signs and symptoms of EVD in conjunction with epidemiological risk factors. However, there is no discussion on the suitability of the product in the EU population.

Post-market data are described, including a Risk Management Plan and a first PSUR. Two residual risks are addressed in the Risk Management Plan. It is recommended to add absence of clinical performance data from clinical patient specimens and the suitability of use of the test in the EU setting.

Overall, although there are some limitations in the overall documentation, specifically concerning the absence of clinical data in clinical specimens and absence of a more detailed description of test performance in the Zaire outbreak of 2018-2019 (as this period comprises the bulk of tests used), the reviewers conclude that this does not prevent final conclusions on the intended use. However, continued post-market surveillance is considered important to

monitor achievement of the intended clinical benefits and safety in accordance with the SOA in medicine.

5. Adequacy of PMPF report(s), where applicable

Concerning the PMFP, the PSUR mentions that the test is an on-market product, with data collected during its time on the market and monitoring of SOA has not highlighted any need for PMPF to take place. The device is considered safe and representative of SOA within a European population, therefore there is no need to initiate the PMPF process at this point.
A Risk Management Report and a PSUR covering the period February 1, 2020 to July 31, 2021 is included to support the post-market experience. The documentation also includes a global Risk Management SOP and a Risk Management Report.
A product safety risk profile, forming the base for assessing the residual risk and the benefit-risk analysis is included. The benefit of the product is considered high, providing rapid identification of patients with possible EVD. On the other hand, the risks are also considered high. Although the projected probabilities of harm are considered remote, the potential consequences are high. The criteria applied for the benefit-risk focus therefore on the literature to determine the benefits and confirmation that these benefits outweigh the risks. These are formulated as: fast turn-around time, high sensitivity, simple sample processing, different sample acceptance, dual target design, impact on biosafety, easy/rapid workflow.
Based on the above the residual risks and the post-launch monitoring plan, including a post-launch data collection and risk monitoring, risk assessment and design and process changes. Results are discussed in the report. A short post-market surveillance summary is included.

A PSUR is included covering the period post 2018-2019 outbreak.

Some observations were noted by the reviewers and are, if applicable, discussed in the recommendations. These include:

- Overall, the post-launch monitoring which is apparently inplace since 2016 indicates no specific reported risks.
- The argument that a PMPF is not needed is based on the assumption that the product is safe within a European population. However, specific data in this population is not provided.
- Although post-launch monitoring includes the period of the 2018-2019 outbreak, a dedicated report on this event and the extensive use in not included.
- Regarding the two above mentioned observations it is recommended to add absence of clinical performance data from clinical patient specimens and the suitability of use of the test in the EU setting.
- The IFU mentions that any positive or negative result should be confirmed. Although the probabilities of occurrence of erroneous results are reported to be extremely low, confirmatory data are not discussed.

- The IFU text in the PER should be the valid current version, identical to the standalone IFU. It was noted that the first still included the possibility of a buccal swab.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report

The manufacturer has compiled comprehensive evidence on the analytical and clinical performance of the test to support its intended use. The device has undergone significant in-house analytical testing and a clinical study using contrived samples. The assay's analytes are well documented within scientific literature.

The assay is performed on a fully automated platform. The test is sensitive in this clinical testing and analytical testing substantiated for different serotypes or genotypes. The assay reproducibility is sufficiently addressed. The assay can be used to diagnose or exclude the presence of Zaire EBOV in individuals with signs and symptoms of EVD in conjunction with epidemiological risk factors. The test does not detect other non-Zaire Ebola viruses and no data are provided on the suitability of the test in the EU population.

Overall, it was concluded that the device achieves the intended clinical benefit and safety when used as intended, although the general opinion of the reviewers was that this assayed assay to individuals with signs and symptoms of EVD in conjunction with epidemiological risk factors has probably limited benefit in the EU setting.

Generally, the experts were positive about the content and extent of the submitted dossier. However, there are several recommendations for evaluation of the assay and for improvement of the dossier.

General recommendations:

1. The absence of any discussion on the usability of the test in EU settings is of some concern. It is recommended to provide a comprehensive discussion on this issue, particularly in relation to the described intended use.
2. Although all elements listed in the IVDR requirements were addressed, the dossier lacks an overall assessment of the available data, including an assessment of benefits and risks of the device for the intended use in the EU setting. It is recommended asking the manufacturer to provide an integrated overview, including context relevant for the IVDR (*e.g.,* translation to EU setting). Also missing are the clinical specimens´ data and absence of an evaluation of the test performance during the 2018-2019 should be addressed. If necessary, the IFU should be updated to reflect the additional information.

Specific recommendations:

3. Regarding the analytic performance:
    a. Information on the detection limit regarding plaque forming units (PFU) is misleading and should be presented with caution. Since the assay detects the viral genome irrespective of the infectivity of the virus the information of LoD of 1.0 PFU/ml applies only for this testing arrangement and might be different in real patient samples. If described as such in the IFU, this should be clarified.
    b. The WHO IRP, already well-characterized in several comparator assays, should be included in analytical characterization of the assay.
    c. Stability study as sample hold time between sample addition and cartridge processing, supports stability in a controlled setting up to 5 hours and 35°C. This may not reflect actual day to day practice in the geographic setting and should be reflected on.
4. Concerning the clinical performance: the NPA acceptance criterion is ≥99% with a lower limit of ≥88%. Given the consequences of false negative outcomes, a further justification of the acceptability of this lower limit could be considered, especially in absence of true clinical specimens´ data.
5. Particularly for unpredictable infections like EVD, diagnostic testing is only one part of patient and outbreak management. This is partly addressed in the IFU, but not further discussed in the PER. The manufacturer is recommended to discuss the added value and need of confirmatory data as well as context for this test.
6. Post-market data including a PMPF is important for any IVD, but particularly for tests used in low or unpredictable prevalence settings. For serious diseases such as EVD, missing a positive case may have serious consequences for the patient and its surroundings. If not observed in clinical studies, active surveillance during outbreaks (e.g., 2018-2019) testing and confirming the initial results from clinical patient specimens are critical to improve patient and outbreak management. It is recommended to add absence of clinical performance data from clinical patient specimens to the residual risks in the RMP.
7. It is recommended to request updating the Risk Management Plan, e.g., adding the suitability of use of the test in the EU setting to the residual risks and monitor test performance and safety of implementing the test in EU countries.
8. Comparative data against other platforms are important, since the clinical performance may differ from analytical performance with respect to sensitivity and specificity, depending on several internal and external factors. Benchmarking against other assays is important to gain a more robust and objective insight into the relative clinical performance. Such data either from comparative studies, ring trials and external quality assessment and literature. It is recommended requesting the manufacturer to reflect on this.

3.6 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[4]
Has the Secretariat provided information from stakeholders?
☐ YES ☒ NO
If yes, please summarise the information and how it was taken into account.
N/A

3.7 Divergent positions in case no consensus can be reached

In case no consensus on the views can be achieved[5], please summarise divergent positions
N/A

Please indicate how many of the experts of the panel had divergent views
None

[4] According to Article 106.4 of Regulation (EU) 2017/745, expert panels shall take into account relevant information provided by stakeholders including patients' organisations and healthcare professionals when preparing their scientific opinions.

[5] According to Article 106.12 of Regulation (EU) 2017/745, when adopting its scientific opinion, the members of the expert panels shall use their best endeavour to reach a consensus. If consensus cannot be reached, the expert panels shall decide by a majority of their members, and the scientific opinion shall mention the divergent positions and the grounds on which they are based.