EUROPEAN COMMISSION

View in 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	24/09/2021
Notified Body number	2797
Internal PECP dossier #	IVD-2021-000003
***In vitro* diagnostic medical device**	This test is intended for detection of West Nile Virus (WNV) RNA in plasma and serum specimens (blood screening).

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)*	West Nile Virus (WNV) RNA
P2	function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc*	Detection of West Nile Virus (WNV) RNA in plasma and serum specimens (blood screening)
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.*	Reduce risk of transmission of WNV via infected blood transfusion or organ transplantation
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*	Plasma and serum
P7	where applicable, the testing population *e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range*	Human blood donors and human organ and tissue donors
P8	intended user	qualified clinical laboratory personnel
Technology (T)		
T1	principle of the assay method or principles of operation of the instrument	Qualitative nucleic acid test (NAT) using target capture, target amplification by Transcription-Mediated Amplification (TMA) and detection of the amplification products

	e.g. real-time PCR, qualitative PCR, digital PCR, sandwich immunoassay, competitive immunoassay, immunoturbidimetric assay etc.	(amplicon) by the Hybridization Protection Assay (HPA)

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group

Date of views	12/11/2021
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-3

3.2 Summary of expert panel views

The device is used for the detection of West Nile Virus infection in plasma and serum specimens. The purpose of the device is to determine if a human is acceptable as a donor of blood, tissue, and organ products into recipients. The device is not intended for diagnosis. The technology of the device is a nucleic acid test (NAT) based on amplification by transcription-mediated amplification, and subsequent detection by hybridization. There are no Common Technical Specifications for the West Nile Virus assays specifically, so the manufacturer applied the Common Technical Specifications referred to requirements for nucleic acid amplification techniques with respect to reference materials and qualitative HIV assays. The scientific validity report is based on literature search with relevant keywords. The scientific validity is sound. The analytical performance report contains analysis of all required performance parameters for the intended use of the device. The performance characteristics are in line with the common technical specifications for HIV nucleic acid amplification techniques that the manufacturer uses in view of lack of common technical specifications for WNV nucleic acid amplification. The clinical performance report contains analysis of all required performance parameters for the intended use of the device. The clinical performance parameters are suitable for the intended use of the device.

Generally, the expert views were in line with each other. The overall opinion on the content of the submitted dossier was positive.

Three general issues were, however, noted by the experts.

First the generalizability to EU setting. The product is a US developed assay under FDA guidance and regulation. It is not clear to what extent this fits with EU guidance and regulations. The manufacturer has not made an attempt to make this comparison.

An additional point was the absence of a package insert describing the intended use, the methods, claimed performance characteristics etc. which is important information as benchmark for the evaluation of the dossier. Although reference is made, the package insert was not included. The experts recommend asking the manufacturer to provide this package insert.

A third general observation was the absence of an integrated overview by the manufacturer, providing integrated context, and analyses of the analytical and clinical performances of the test over time with a critical discussion on the benefits but also the limitations. The dossier would benefit of such overview.

Regarding the content of the dossier, the experts expressed the following views.

For the application of this test, molecular screening of possible blood or tissue donor materials the submitted dossier provide extensive analytical performance data in both serum and plasma sample with different methods for anticoagulation, storage conditions and stability effects etc. This is generally a comprehensive approach. It was however, noted that test performance in whole blood was not considered, although some screening laboratories may prefer screening on whole blood given the reported higher sensitivity for WNV.

Since the intended use also limits to serum and plasma, the possible consequences of excluding whole blood should be discussed.

In addition, test performance was tested in (dead and living) cadaveric specimens. In all analyses sensitivity and specificity are high and acceptable for the intended purpose of the test as screening assay. Given the expected low prevalence of positive samples, particularly specificity is of major importance as the risk of false positivity increases with decreasing prevalence.

Analytical performance against both lineage 1 and lineage 2 is tested. Sensitivity and specificity against both were comparable, as was the limit of detection (LOD) around 12-13 copies/ml. Several experts however, commented on the dating of literature search, with no references beyond 2012 and the uncertainty whether the targets used were in agreement with current circulating virus strains, since studies in the dossier were not dated.

It is recommended asking for clarification on this part.

Clinical performance of the test is relatively limited. The question is whether this is important given the intended use. A limitation noted by the experts in this context however, the absence of comparative data versus other platforms generally used for this screening purpose. Only one other platform was used only to be applied in case of discrepancy between testing sites. The absence of comparative data is considered a missed opportunity, 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 platforms is important to gain a more robust and objective insight into the relative clinical performance. Such data either from comparative validation studies, ring trials, external quality assessment and updated literature reviews of which the dossier should benefit is missed. The experts recommended asking the manufacturer to contemplate on this.

A similar point was the relative lack of post market data. The product has a long history, with a reported introduction into the market since 2006. Post market data were, however, only available for 2019, without any distribution or used data. To gain a more solid understanding on the clinical performance and quality over time, the experts recommended asking the manufacturer to provide more extensive post market data.

In summary, overall, the experts were positive about the content and extent of the submitted dossier. There were, however, a few recommendations of which the dossier could substantially benefit is clarified. These 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]
The manufacturer has established the scientific validity for the WNV assay through a search of peer-reviewed literature, including articles and websites covering epidemiological studies, disease prevalence, and relevance of WNV as a transfusion transmitted infection and the implementation of NAT methods for donor screening. The manufacturer has made a comprehensive literature review of the peer-reviewed scientific literature using keywords relevant for this project. However, these studies are not included in the references provided. Since the implementation of WNV screening, several cases of transfusion-transmitted infection have been documented and reported by the US-CDC, which is reflected in the indicated references. This is a legacy device with well-established scientific validity. The data generated from analytical and clinical performance studies of the assay are the basis for demonstrating clinical evidence. The scientific validity supports the need for screening blood for WNV due to the risk of transfusion transmission as well as the NAT methods are the most appropriate for blood screening compared with other current diagnostic methods.
2. Expert views on the analytical performance report[2]
The manufacturer demonstrates the analytical performance of the device in relation to specimen type with the following performance parameters: Specificity, sensitivity, sensitivity in different anticoagulants, sensitivity in pooled specimens, sensitivity in stored specimens, sensitivity in cadaveric whole blood. i. The manufacturer has evaluated the specificity and sensitivity of the device in specimens collected in various anticoagulants and serum in order to determine the effect on the specificity and sensitivity of the device. It was made using five unique donor samples, 10 anticoagulant types and serum, and two different reagents lots (18 and 19). The specificity and sensitivity were 100%. ii. The manufacturer has evaluated the sensitivity of the device in specimens collected in various anticoagulants and stored at different temperatures, according to the conditions specified in the package insert. WNV was detected in 100% specimens, indicating its stability in all recommended anticoagulants. iii. The manufacturer has evaluated the sensitivity of the device in detecting WNV viral RNA in specimens collected in various anticoagulants and put through multiple freeze/thaw cycles. No effect of anticoagulant or freeze/thaw (up to four cycles) was observed on the sensitivity of the device. iv. The manufacturer has evaluated the sensitivity of the device in detecting low levels WNV viral RNA in pooled specimens stored at different temperatures for an extended period of time. The device was able to detect low levels of West Nile viral RNA in 1:16 pooled specimens stored at different extreme conditions.

[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

v. The manufacturer has evaluated the sensitivity of the device in detecting WNV viral RNA in specimens stored for up to 9 months at -20°C and up to 15 months at -70°C in four different anticoagulant collection tubes. The device was able to detect WNV viral RNA in samples stored as previously described, with reactivity rates from 98.6 to 100%.

vi. The manufacturer has evaluated the detection of WNV in cadaveric whole blood collected with EDTA and without any anticoagulant. The device was able to detect WNV with reactivity rates >99% in plasma samples and >97% in serum, both stored for 11 days.

The manufacturer demonstrates the following analytical performance parameters of the device.

i. The reproducibility was evaluated for inter-instrument, inter-operator, inter-lot, inter-day, and intra-run variability. The device showed a high reproducibility across operators, instruments, reagent lots, and days tested using a range of panel types with negative and both high and low copy levels of WNV. Also, the reproducibility was evaluated in cadaveric specimens, showing a high reproducibility too.

ii. The device was able to detect lineage 1 and lineage 2 WNV genetic variants in samples comprised of dilutions of WNV cell cultured virus and RNA transcripts. The device was evaluated to detect WNV in naturally infected blood plasma samples from donors confirmed to be WNV positive (352 specimens). The clinical sensitivity was evaluated in two platforms and was 67% and 65.9%. Further, the device was evaluated to determine detecting WNV prior to seroconversion. This detection of WNV RNA occurred 14 to 12 days earlier than the detection of IgM. The device was evaluated to detect WNV RNA in cadaveric specimens. The sensitivity and specificity were 100%, demonstrating that the specificity and sensitivity were not affected. The manufacturer evaluated the performance of the Internal Control for the device under inhibitory conditions. The Internal Control proved to serve as an effective control for false negative results from problems in the reagent preparation, target capture, amplification, or detection steps.

iii. The manufacturer has evaluated the specificity of the device in normal blood donor plasma samples. 3933 negative samples were tested, and the specificity was 100% (Study Protocol P10236-0306). The manufacturer has also evaluated the specificity of the device using high titer samples (Study Protocol P10236-0307-TP). 354 negative samples and 354 high titer samples were tested in an alternating negative-high titer distribution pattern. The specificity was 100% demonstrating no cross contamination in adjacent samples or reaction tubes. The manufacturer has evaluated the device's sensitivity and specificity with different endogenous interferents (Study Protocol P10236-0308). The sensitivity and specificity for samples containing blood-borne pathogens other than WNV or exposed to flu or HBV vaccines were 100%. Also, specimens spiked with Hepatitis G Virus (HGV), St. Louis encephalitis virus (SLEV), Murray Valley encephalitis virus (MVEV), Japanese encephalitis virus (JEV), Yellow Fever Virus (YFV) and Dengue viruses (serotypes 1-4) did not show any reactivity. The manufacturer has evaluated the device's sensitivity and specificity in specimens from patients with autoimmune disorder and other diseases. The sensitivity and specificity for samples from donors with autoimmune disorder and other diseases were 100%. The manufacturer has evaluated the device's sensitivity and specificity in specimens contaminated with bacteria, yeast, and fungi. The sensitivity and specificity were 100%. The manufacturer has evaluated the device's sensitivity and specificity in hemolyzed, icteric, and lipemic Specimens. The device was 100% specific and

100% sensitive in analytical samples containing concentrations of hemoglobin, bilirubin, albumin, and lipids. The device was also 100% specific and 100% sensitive in clinical specimens that contain hemolyzed, lipemic or icteric plasma. This study demonstrated that specimens containing potentially interfering substances did not affect the specificity or sensitivity of the device. The manufacturer has evaluated the specificity and sensitivity of the device in normal donor specimens to generate control data for comparison purposes for the donor and donation factor studies. The sensitivity and specificity were 100%. The manufacturer has evaluated the specificity and sensitivity of the device in pools of specimens from donors with putative interfering substances (test pool) as compared to pools of specimens from normal donors (control pool). The sensitivity and specificity were 100%, demonstrating that the presence of multiple factors had no differences in specificity or sensitivity in pooled specimens from donors containing the donor and donation factors when compared to the control pools.

iv. The manufacturer has evaluated analytical sensitivity and limit of detection (LOD) of the device for detection of WNV viral and transcript RNA. A lineage 1 viral stock standard and two in-house WNV transcripts for lineage 1 and lineage 2 were studied and diluted from 100 to 0 copies /ml. The limit of detection was 11.9 c/ml, 12.9 c/ml, and 12.0 c/ml respectively for viral standard and in-house lineage 1 and lineage 2 transcripts.

v. The manufacturer describes the validation of the analyte cut-off calculation using a statistical analysis of sensitivity and specificity. The optimal cutoff value was determined using ROC curves of sensitivity and specificity data. The data confirmed that the cutoff calculations for the WNV assay are optimally balanced to ensure sensitive and specific assay performance.

Regarding parameters that were omitted (linearity/measuring range, trueness, accuracy, diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, and likelihood ratio) the manufacturer has considered not applicable or relevant for a qualitative assay.

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

The clinical specificity was 100% for 16-sample pools and 100% for individual donor samples from whole blood donations. The device is thereby suitable for its intended purpose and demonstrates its clinical utility.

The clinical sensitivity of the device was 99.1% in neat samples and 98.2% in diluted samples

The manufacturer has evaluated the reproducibility and repeatability studying the following sources of variation: within runs, between runs, between operators, between sites/instruments, between reagent kit lots, and between days. 100% agreement was found in the negative, low moderate positive, and high moderate positive panel members. However, 98.1% and 51.9% agreement were found in low positive and high negative panel members respectively. Total variability with WNV concentrations $\geq$ 95% LOD was $\leq$15.4%.

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

Post market surveillance report includes annual surveillance review of the complaint management system, customer preference surveys, customer satisfaction surveys, ongoing stability studies, similar product reviews and performance reviews. On annual basis are performed:

Annual surveillance review of records from complaint management system including details of any PHSCs (Potential Health and Safety Issues), identified trends, Regulatory report. The annual surveillance report of 2019 is discussed, including 4 complaints relating to the WNV assay, with no new risk; 3 deviations (nonconformances), without any trends or impact on product safety; 33 inquiries relating to the assay, without any trend. There were no corrective and preventive actions (CAPAs); there were 2987 training records; there was 1 incident report of a false negative test. Regarding risk assessment and conclusion, it is concluded that surveillance data did not identify any changes in the product risk profile and acceptability and no new risks were identified.

Review of publicly available information from similar devices showed 9 events that were not of relevance to the product under assessment.

A customer survey report did generate many suggestions for improvement, but not for improvement to product safety.

Stability studies are continuously ongoing, serving as early warning of potential issues of reagents on the market.

Performance data against relevant similar devices are not described.

Regarding current state of the art use of redundant primers in the amplification systems is used to mitigate the risk of genetic mutations affecting overall performance of the assay. Detection of these mutations, relies on complaints for discrepant results as part of the complaint process.

The possible adaptation of targets based on customers' complaints is a post-hoc and passive approach. It is unclear why a proactive approach based on (literature) surveillance and virus evolution is not considered.

There were no manufacturers sponsored clinical trials in 2019.

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 not intended for diagnosis but for detection of WNV RNA in plasma or serum samples to determine if blood products or tissues can be safely donated/transplanted into recipients. The device is a legacy device, and a substantial amount of clinical data comes from previous versions of the device. Clinical performance data was gathered from different sites. The expert´s view is that overall sufficient clinical evidence for the intended use of the device was presented to support safety and intended clinical benefits, although some issues for further consideration were expressed by the expert panels as addressed in section 3.2.

2. The literature search methodology, protocol and report
Methodology for the literature search supporting the scientific validity is clearly and comprehensively described. The review is limited to the period 2012-2016. There is no clarification for these limits. Despite this, for the intended purpose of the assay, the review on scientific validity is adequate. References supporting the scientific validity of the WNV assay are not included in the reference list. Particularly literature comparing the manufacturers' assay and platform with other products on the market is missing. Although literature on virus evolution is included, how this is used to upgrade the manufacturers' assay is not described (see also post market experience). The possible adaptation of targets based on customers' complaints is a post-hoc and passive approach. It is unclear why a proactive approach based on (literature) surveillance and virus evolution is not considered. The manufacturer doesn't include a literature search report with relevant publications in peer-reviewed journals. This literature search report must include publications that support the scientific validity for the use of NATs generally, and publications that support the WNV NATs specifically for donor screening. The manufacturer either includes publications with a less favourable or controverting findings, and either other published experience gained from routine diagnostic testing has been made in the literature search.
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 technology used, a nucleic acid test, (NAT) in plasma or serum samples from human donors is a qualitative molecular method with WNV RNA target amplification by Transcription-Mediated Amplification (TMA); and detection of the amplification products (amplicon) by the Hybridization Protection Assay (HPA). This method is widely used and generally accepted. For screening samples for WNV RNA a qualitative assay is appropriate. Nucleic acid test technology has been used in blood donor screening to decrease the "window period" between initial infection and the antibody detection for over a decade and is considered "state of the art". The use of this technology is fit for purpose. Performance of safety of the device is addressed. Claims as should be covered in the package insert cannot be evaluated, since the package insert was not included, despite several references to it.
4. Acceptability of clinical evidence (clinical data and performance evaluation results) against state of the art in medicine
Clinical evidence is presented in both the analytical and performance documents. For the purpose of a screening test, the extensive dataset provided to assure analytical precision is sufficient. Particularly the analytical dataset has provided extensive information on sensitivity, specificity, reproducibility, and stability. Clinical performance chapter as well as the post market chapter is less extensive. As mentioned under 3.2 there is no comparison of the test other systems on the market for the same intended use. Also the absence of dated reporting precludes a final conclusion on the question whether the intended clinical benefits and safety were achieved according to the state of the art in medicine.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report
The manufacturer has compiled comprehensive evidence on the clinical performance of the assay to support its intended use. The device has undergone significant in-house analytical testing as well as clinical trials at various clinical sites within the US. The assay's analytes are well documented within scientific literature. The assay is performed on a fully automated platform. For plasma and serum tested individually or in pools. The assay is highly sensitive in clinical testing and analytical testing of the Health Canada Reference Standard and through testing of genetic variants. The assay is highly reproducible across testing sites, operators, reagent lots, testing days, and runs. Testing of a commercially available seroconversion panel demonstrate that the device could reduce the pre-seroconversion window period WNV detection when compared to an antibody test. The assay can be used to screen organ and tissue donors, including cadaveric (non-heart-beating) donors, and demonstrated high specificity, sensitivity, and reproducibility of cadaveric plasma and serum specimens. It can be concluded that the device achieves the intended clinical benefit and safety when used as intended. The report could benefit from: Inclusion of the package insert/instructions for use and a comprehensive list of up-to-date literature used for scientific validity. In summary, overall, the experts were positive about the content and extent of the submitted dossier. There were, however, several recommendations which the dossier could benefit from. These include in general sense: - The generalizability of the dossier to the EU market with reference to EU guidance and regulation regarding the blood safety in blood and tissue donations, but also epidemiology and screening practices - The absence of a package insert, relevant for benchmarking the evaluation of the content of the dossier. - The absence of an integrated overview by the manufacturer discussing context, performance benefits and limitations. Content specific the experts recommended consideration of the following issues: - The limitation of the test to serum and plasma, thus excluding whole blood (this links to the generalizability) - The absence of up-to-date literature references and uncertainties whether used targets are agreement with current circulating virus strains (link to generalizability and discussion on benefits and limitations). Data from clinical performance studies and in particular the absence of discussions on comparison with other molecular platforms generally used, performance of the test in ring trials or external quality assessments and relevant literature. In this context the availability of a post market report of 2019 only, without distribution and/or user data over time hampers a solid understanding of clinical performance over time. Such information might be beneficial in the discussion on extrapolation to EU market.

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.
TEXT

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
There were no divergent views.

Please indicate how many of the experts of the panel had divergent views
Not applicable

[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.