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-2021-000005
***In vitro* diagnostic medical device**	The device is a qualitative in vitro nucleic acid screening test for the direct detection of Zika virus RNA in human plasma.

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)*	Zika Virus RNA
P2	function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc*	This test is intended for use to screen donor samples for Zika virus RNA in plasma samples from individual human donors, including donors of whole blood and blood components, and other living donors. This test is also intended for use to screen organ and tissue donors when donor samples are obtained while the donor's heart is still beating.
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.*	Zika virus transmission in blood transfusion
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
P7	where applicable, the testing population *e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range*	Living donors of whole blood and blood components and other living donors. Organ and tissue donors.
P8	intended user	Trained laboratory professionals who are proficient in using the automated platform
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.*	Real-time PCR

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group

Date of views	09/12/2021
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-5

3.2 Summary of expert panel views

The device concerns a qualitative *in vitro* nucleic acid test (NAT) for the detection of Zika virus RNA (ZIKV RNA) in human plasma of whole blood and blood components and other living donors. This CE-marked device is on the market under the In Vitro Diagnostic Directive (IVDD) since December 2019. The assay is intended for use on prespecified systems. The test is intended for use to screen individual samples from human donors, including whole blood and blood components, as well as in pools of not more than 6 individual samples. The test is not intended for use as an aid in diagnosis of ZIKV infection, for use on samples of cord blood or for use on cadaveric blood specimens.

The dossier includes a Performance Evaluation Report and product information, *i.e.* a package insert/Instruction for Use (IFU) describing intended use and rational, non-clinical and clinical performance evaluation. Procedures, safety conditions and precautions, as well as limitations are clearly described, including the short persistence of RNA in blood products, the potential of mutations affecting performance or the need for correlation studies when switching to a different platform.

The rational for the intended use of the assays (screening of plasma from blood donors or other living (tissue) donors) is justified on the observations that: 1/ ZIKV can be transmitted via transfusion and 2/ most ZIKV infections are asymptomatic. However, ZIKV is non-endemic in the EU and it is unclear whether EU guidelines and regulations concerning safe use of blood products and tissues consider the need for ZIKV screening. For the purpose of this procedure, the scientific validity is fulfilled if the test is suitable to screen blood donations. How frequent ZIKV infection occurs in Europe and if, for example, screening is done only temporarily in the summer season or regional in Europe or for preparedness only is another question. However, in absence of an actual (albeit minimal) risk, the chances of false positivity increase. The risk-assessment of ZIKV in blood donors is based on data from outbreak settings and epidemic regions, which are different from the EU setting where incidental infections are reported.

An ECDC annual report on ZIKV surveillance (2019) reported 3 autochthonous vector-borne cases of ZIKV disease in France in that year. These are up to now the only reported autochthonous ZIKV disease cases acquired via vector-borne transmission in the EU/EEA.
This implies an incidental risk of a viremic donor that would have contracted the infection while in a geographic region with ZIKV risk. While it is known that the duration of viremia is short lived in blood samples, this risk of transmission through blood or tissue donations becomes theoretical. Additionally, the risk for serious disease associated with ZIKV infection are mainly linked to infections in pregnant women.

The performance of the test is evaluated in analytical and clinical performance studies. Clinical evidence consisted of scientific validity, analytical performance and limited clinical performance. The measurements and analyses were sufficiently acceptable in demonstrating the ability of the ZIKV NAT to correctly classify the results based on the samples tested. The reported performance evidence is suitable for the intended use of the *in vitro* diagnostic (IVD).
Analytical specificity is evaluated against other arthropod-borne viruses and *Treponema pallidum*, HIV, HBV and HCV, but not but not against other viruses that may be more prevalent like EBV and CMV.
All studies are performed at US sites. Concerning clinical performance during the ZIKV epidemic, in almost 5 million donations, 30 were tested positive. In an outbreak setting positivity rate was 0.004%. The positive predictive value (PPV) in a low prevalence area was 60.9% compared to 96.2% in a high prevalence area. The implication for the EU setting needs to be discussed.
A concise but comprehensive summary of the risk management plan is provided. Given the expected minimal risk in the EU setting, it is important that measures proposed to mitigate the identified risk, including false negativity at the limit of detection (LoD), are adequately identified and described in the IFU. Post market surveillance data and plans are missing.

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 not or insufficiently addressed by the manufacturer. Recommendations from these observations are listed under 3.5.

The following general issues were, however, noted by the experts.

- First, the absence of any discussion on the generalizability of the test to the EU setting. Given the epidemiology of ZIKV, mainly being imported infections by travellers with incidental autochthonous transmission, contamination of EU donors is likely to be a minimal and transfusion risk is poorly substantiated. A discussion on this issue is important, particularly where it comes to relevance for blood safety regulations.
- An additional observation was the organisation of the dossier. Although the dossier systematically addressed all IVDR requirements, for the future it is recommended to organize the dossier in a more accessible structure. Related to this was a general observation of the absence of an integrated overview, providing context (*e.g.* translation to EU setting), and analyses of the analytical and clinical performances of the test over time with a critical discussion on the benefits but also the limitations (*e.g.*, absence of post market data) and translation of this into the IFU, particularly describing specific performance information for use the EU area (*e.g*. impact on the PPV).

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

- For the application of this test (molecular screening of possible blood or donor tissue materials from circulating blood), the submitted dossier provide analytical performance data in plasma samples and claims sensitivity and specificity in single sample as well as in plasma pools. The latter are not specified in the dossier or the IFU (including the number of samples per pool). Regarding the IFU, the reviewers also noted that performance data from live tissue donors were not presented in the dossier. The reviewers also noted that particularly in low endemic regions like the EU, blood screening is not the only measure to assure blood safety. Such disclaimer is missed in the IFU.
- Analytical performance was not systematically tested against ZIKV lineages from different geographic origins. Several experts commented on absence of meaningful data from different lineages as well as a clear reporting of dating of the studies and used targets leading to uncertainty whether the targets used were in agreement with current circulating virus strains.
- Clinical performance of the test is limited, with one reproducibility study and one retrospective study conducted in the US. The question is whether this is important given the intended use ad screening assay. A limitation noted by some experts in this context was the absence of comparative data versus other platforms generally used for this screening purpose, even if the comparison with one other platform frequently used for this purpose was performed. 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 platforms is important to gain a more robust and objective insight in to the relative clinical performance. Such data either from comparative studies, ring trials or external quality assessment and literature of which the dossier should benefit is missed.
- Overall analyses of 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 in the EU setting, the risk of false positivity increases. If not observed in clinical studies, such data should come from post market experience. Post market data were not included since the manufacturer did not recognise the need. This position is not acceptable since post market and risk management plans are essential to evaluate the benefits and risks of implementing the screening assays in EU countries.

In summary, overall, the experts were positive about the content and extent of the submitted dossier. There was however a concern regarding the general use of the test in EU settings. Also, a number of 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)

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 and structured 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. The manufacturer has made a comprehensive literature review of the peer-reviewed scientific literature using keywords relevant for this project. The search strategy and protocol for the literature search is for the shortly described, covering the period 2010-March 2021; selected articles ranged from 2017-2021, compared the system with other systems and different geographic reactions, albeit not EU regions. For potential risk for the EU, reference is made to ECDC risk assessment of 2019, concluding that 2 mosquito vectors that have been shown to be competent for ZIKV: *Aedes albopictus* and *Aedes japonicas* are found in the region. However, vector competence is lower compared to *Aedes aegypti*, thus the risk of mosquito-borne transmission of ZIKV is low. Risk is mainly related to travel. Reference is made to ECDC position on prevention of risk of ZIKV transmission, where ECDC suggests considering the restriction of blood, tissues and cells from areas with ongoing transmission. However, under special circumstances, substances of human origin may be imported and tested for ZIKV. NAT testing in areas without active transmission is an option for prevention of ZIKV transmission. The manufacturer has thus provided an EU perspective. However, it does, not reflect on the true risk assessment in the EU region. The benefit-risk assessment provided is of relevance to the non-EU region but might be different in the EU region.
2. Expert views on the analytical performance report[2]
The analytical performance report gives an overview of the analytical performance studies with reference to IVDR requirements. Reporting is tabular with reference to individual studies in annexes. For more details on objectives, preparation of test panels, testing procedures and results, reference is made to individual studies. This precludes an efficient evaluation of the many tests performed and validity of the methods and results. Limit of quantitation with measuring range and linearity is not tested, because the test is qualitative. The manufacturer demonstrates the analytical performance of the device in relation to specimen. The LoD at 95% probit analysis, performed using independent dilution series of an in-house culture of a prototype ZIKV strain (posteriorly calibrated with the WHO standard), was 8.1 copies/mL or 16.2 IU/mL (calculated on two different batches of the device). The specificity was determined on a panel of

[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

microorganisms, including mostly other arboviruses (*e.g.* flaviviruses) and common blood-borne viruses, and potential interferences with exogeneous and endogenous substances commonly found in blood donations were evaluated. Both were found satisfactory. The performance evaluation was conducted using another NAT method on 100 negative and 99 positive serum samples (from Americas) with correlated results. The evaluation of the different biological matrices (with EDTA, CPD, CP2D and PPT plasma) was performed and found to be equivalent.
Detection performed on a limited panel of clinical samples (n=5) with a viral load approaching the LoD (13.6 copies/mL) was satisfactory.
The evaluation of the analytical sensitivity was performed on a panel of a restricted number of clinical samples (n=25) collected mainly for the Americas was also satisfactory. However, this evaluation remains limited and does not include the other genotypes/lineages.
Since the device is a qualitative test and only reports the presence or absence of the test target, the manufacturer did not conduct studies to determine analytical performance for limit of quantitation, measuring range, and linearity.
Pooled analysis was reported for a maximum of 6 pools from aliquots of donors.
Except for a single sample from French Polynesia, all other samples were only from South America. No data from Asian or African ZIKV genotypes were found in the dossier.

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

Clinical performance report is based upon historical data since studies prior to IVDR enactment, which is understandable. Statement of unmet medical, public health, or laboratory need is fully justified by stating the test provides a novel capability to detect ZIKV RNA and thereby provides heightened protection from transfusion-transmitted ZIKV infection for recipients of donated blood components or products and will further improve the safety of the blood supply. However, this depends upon the risk assessment.
No specific clinical performance studies were conducted. Two clinical registration studies are referenced: one reproducibility study and one prospective study evaluating the specificity of the test on the designated system for the screening of blood donations. The first study supported reporducibility across lots, sites, days, and batches with agreements over 91%. In the specificity study, comparison of reactive samples with an alternative NAT and IgM serology provided high specificity (>99.99%). Both of theses clinical registration studies focused on samples obtained from the Americas.
During the reproductibility study which was performed both in continental USA (lower ZIKV prevalence, indicated as 0.004%) and in Puerto Rico (higher prevalence, indicated as 0.74%), the determination of the PPV (initially requested by the FDA) was found coherent with 60.9% and 96.2%, respectively, based on confirmed reactive samples with alternate methods. The specificity value was >99.99 %.
Performance in pooled samples is not discussed. Minipool testing was mentioned in one report and referenced in one publication, but not included in the dossier as such, or detailed in the IFU.
The device is thereby suitable for its intended purpose and demonstrates its clinical utility, at least for single sample use.
Clinical performance report is based upon historical data of studies prior to IVDR enactment.

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

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

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 ZIKV RNA in plasma samples to determine if blood products, tissue or organs can be safely donated or transplanted into recipients. The device is a legacy device. To this aim, the manufacturer has compiled comprehensive evidence on the clinical performance of the assay to support its intended use, as detailed in the Clinical Validation Plan and reported in the Clinical Performance Report and Clinical Validation Report. Regarding the clinical performance, the manufacturer mentions that no studies have been executed for the assay under IVDR that would require referencing under Annex XIII Section 1.2.1. In addition, it states that the demonstration of compliance to Annex XIII Section 2 is not applicable because the studies that generated substantial and relevant data predate IVDR enactment and therefore have been provided as other sources of clinical performance data. The manufacturer gathered information from other sources of clinical data including review of the literature and two clinical performance studies to evaluate the reproducibility (across lots, sites, days and batches), or to evaluate the specificity, respectively. However, both of them were conducted only in the Americas and the performance evaluation of the test regarding the detection of other genotypes/lineages of ZIKV (Asian and African) remains limited. Only two peer-reviewed articles evaluating the performance of the device in Asia and Oceania were indicated. There is no description on the development of the device since first introduction. There is reference to a design history file. As far as ascertainable from the dossier, however, the design is not exactly identifiable, *e.g.* target genes of the primers and probes. 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 issues for consideration were expressed by the expert panels as addressed in section 3.2. Of particular concern are the missing performance data from non-endemic EU settings.
2. The literature search methodology, protocol and report
The methodology for the literature search supporting the scientific validity was clearly and comprehensively described. For the intended purpose of the assay, the review on the scientific validity appears adequate. A total of 7 peer-reviewed articles describing the clinical performance of the test was summarized, in addition to 2 conference abstracts. No publication reporting less favourable findings or controverting findings was identified by the manufacturer. Most of the cited literature focused on a limited geographical area of investigation (*i.e.* the Americas) expected for two publications (Asia and Oceania), which did not allow to have an evaluation of the clinical performance on other ZIKV genotypes/lineages (*e.g.* African ZIKV). Although literature on virus evolution is included, and its' short description in the RMP to adapt to state of the art assays. It is not clear whether this knowledge was actually used to optimise the assay for current use, including the EU

setting (see 3.5). The absence of post-market information in this respect is a limitation for the overall understanding of the benefits and risks of this assay for use in the EU setting.
Literature comparing the manufacturers' assay and platform with other products on the market is included in references, but is not discussed. In the dossier, only one platform was evaluated. In the literature, review reference is made to another comparison with 2 NAT assays for diagnostic application.
The literature review does not discuss virus genetic variations.

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 is a qualitative nucleic acid test (NAT) to detect ZIKV RNA by RT-real time PCR in plasma samples from human donors, after a nucleic acid extraction and purification step. These qualitative assays are widely used and generally accepted for screening. Performance of safety of the device is addressed. The methodology has been used in blood donor screening to identify and exclude donors with ZIKV viremia. For this purpose, a qualitative assay is appropriate. Performance of safety of the device was correctly addressed.
The assay under consideration has no significant innovations and has been in use in the market in Europe since December 2019.

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. For a screening test, the extensive dataset provided to assure analytical precision is sufficient. Particularly the analytical dataset has provided extensive information on LoD, specificity, sensitivity, correlation and performance of the assay under investigation with a peer assay, cross reactivity, endogenous and exogenous interference, reproducibility and stability of samples and reagents. However, the evaluation for the detection of the different genotypes/lineages remains limited.
The clinical performance evaluation is less extensive. Post market data are not available. As mentioned under 3.2, there is only one comparison of the test with another commercial test system for the same intended use.
Overall, the reviewers were of the opinion that this does not prevent final conclusions on the intended use. However, continued postmarket surveillance was considered important to monitor achievement of the intended clinical benefits and safety in accordance 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 tested individually or in pools. The maximum pool size is not specified. The assay is highly sensitive in clinical testing and analytical testing substantiated for a limited number of genotypes/lineages. The assay reproducibility is sufficiently addressed. The assay can be used to screen organ and tissue donors, including live tissue donors demonstrating high specificity, sensitivity, and reproducibility of plasma specimen.
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 ZIKV screening assay to analyse donors 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. The manufacturer is recommended to provide a comprehensive discussion on this issue, particularly regarding the significance for (EU) blood safety regulations.
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 better structure the dossier, with an integrated overview, providing context (*e.g.* translation to EU setting), analyses of the analytical and clinical performances of the test over time with a critical discussion on the benefits. Also missing post market data and translation of this into quantitative information in the IFU should be addressed.

Specific recommendations:

1. For the application of this test, analytical performance (sensitivity and specificity) was performed in single plasma samples as well as in pooled plasma samples. However, the latter are not specified in the dossier or IFU, which should be updated with this information for the latter.
2. The dossier does not include assay performance data in plasma from live tissue donors materials. The manufacturer is recommended to discuss the acceptability of extrapolating performance results from plasma pools to individual plasma samples.
3. The dossier does not include assay performance data for other (Asian, African) genotypes, except for one publication focused on Asian strains. If data are not available the intended use should be restricted accordingly, or adequate substantiation should be provided.
4. Particularly in low endemic regions like the EU, blood screening is not the only measure to assure blood safety. Such disclaimer is missed in the IFU.
5. The absence of post market data is not acceptable. Given the expected low prevalence of positive samples in the EU setting, the risk of false positivity increases. If not observed in clinical studies, such data could come from post market experience. It is recommended to request post market and risk management plans from the manufacturer to better evaluate the benefits and risks of implementing the screening assays in EU countries.
6. One other platform, frequently used for this purpose was compared to. 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 platforms is important to gain a

more robust and objective insight in to the relative clinical performance. Such data either from comparative studies, ring trials or external quality assessment and literature of which the dossier should benefit is missed or limited. 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.
Not relevant

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 relevant.

[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.