EUROPEAN COMMISSION

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

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

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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	15/10/2021
Notified Body Number	2797
Internal PECP dossier #	IVD-2021-000006
***In vitro* diagnostic medical device**	This test is a qualitative in vitro test for the direct detection of chikungunya virus (CHIKV) RNA and dengue virus (DENV) serotypes 1-4 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)*	Chikungunya virus (CHIKV) RNA and dengue virus (DENV) RNA
P2	function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc*	The test is intended for use to screen donor samples for CHIKV RNA or DENV RNA alone or to simultaneously screen for both CHIKV and DENV RNA in plasma from individual human donors, including donors of whole blood, 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.*	Chikungunya virus (CHIKV) and dengue virus (DENV) 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, blood components and other living donors. Organ and tissue donors.
P8	intended user	Trained laboratory professionals who are proficient in using 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	10/12/2021
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-6

3.2 Summary of expert panel views

The device concerns a qualitative in vitro nucleic acid test (NAT) for the detection of dengue virus (DENV) RNA and chikungunya virus (CHIKV) RNA in human plasma and other living tissue donors. The assay is intended for use on prespecified systems. Test can be used to analyse individual samples as well as sample pools. The test is not intended for use as an aid in diagnosis of DENV or CHIKV infection, for use on samples of cord blood or for use on cadaveric blood specimens.

Common specifications for DENV and CHIKV screening tests are not yet defined.

A package insert/ instruction for use (IFU) describes intended use, non-clinical and clinical performance evaluation. Procedures and limitations are described, including the potential of mutations affecting performance, the need for correlation studies when switching to a different platform. The claimed limit of detection (LoD) for DENV at 95% probit analysis varies between 0.4-1.0 IU/ml for the 4 DENV serotypes. The claimed LoD for CHIKV varies between 6.8-9.3 DU/ml for the 3 different genotypes (Asian, ECSA, WA). IFU presentation lacks however a clear insight on clinical diagnostic accuracy of the test. It is recommended that the manufacturer presents data according to sensibility, specificity, positive, and negative predicted values including 95% confidence interval. Also, the maximum number of samples to be pooled is not specified.

The intended use of the assays is screening of plasma from blood donors or other living (tissue) donors. The scientific validity of this approach depends upon the need assessment. DENV and CHIKV are 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 DENV and/or CHIKV screening.

A comprehensive literature review focusses on different aspects of the test performance of the platform, including one reference from the EU (Spain) where following first autochthonous reports of DENV and CHIKV infection blood screening for both viruses was implemented. No description on the EU epidemiology is provided and thus the rational for using this screening test in test in the EU setting.

Reports from ECDC (2019) mention a substantial number of imported DENV (n = 4020 from 27 countries) and CHIKV (n = 516 from 15 countries) infection by travellers. Autochthonous transmission was reported in 12 patients for DENV (10 vector transmission, 1 sexual transmission, 1 laboratory transmission) in 2019 and 1 in 2021. No autochthonous transmission for CHIKV was reported for these years, although previous outbreaks have shown the potential for autochthonous CHIKV transmission [1].

The performance of the test is evaluated in analytical and clinical performance studies. The analytical performance studies included an extensive set of technical performance verification studies, with 100% specificity, 100% sensitivity down to 3-times LoD, no endogenous or exogenous interference or cross-reactivity to other pathogens. One comparative analysis versus another platform suggested better sensitivity of the test under evaluation.

One retrospective clinical performance study was performed with samples collected in Puerto Rico, showing 100% specificity with no reactive samples. The reviewers noted that this is not in agreement with new Regulation 2017/746. The manufacturer did not perform prospective or retrospective clinical performance study in Europe. In this context, the manufacturer's conclusions from the risk assessment that the overall medical benefits of the product outweigh and justify the overall residual risk acceptability cannot be fully supported as details on identified risks and strategies to mitigate them, particularly those related to clinical performance and feasibility for the intended use in the EU setting are not discussed. 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.

[1] Autochthonous transmission of chikungunya virus in mainland EU/EEA, 2007–present (europa.eu)

The following general observations were noted by the experts.

First the absence of any discussion on the generalizability of the test to the EU setting. Given the epidemiology of DENV and CHIKV, both mainly being imported infections by travellers with incidental autochthonous transmission and outbreaks, contamination of EU donors is likely to be a minimal, transfusion risk is not 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 positive predictive value).

Specific observations noted by the experts were the following.

For the application of this test, molecular screening of possible blood or donor tissue materials 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 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.

The analytical performance is considered good in terms of LoD with testing of individual genotypes of CHIKV and serotypes of DENV. The panel of “clinical” samples is however limited to only 1 artificial sample for West Africa CHIKV and 1 cultured isolate for ECSA CHIKV. The cited literature reports of 2 publications on the detection of CHIKV and/or DENV in Asia. No publication or data are presented on African CHIKV, and limited/no data on American strains.

Clinical performance of the test is limited to one retrospective study. The question is whether this is important given the intended use ad screening assay. A limitation observed by the experts is the absence of comparing data with other assays generally used for this screening purpose. 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 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 reviews of which the dossier should benefit is missed.

Overall 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 in the EU setting, the risk of false positivity increases. If not observed in clinical studies, such data should come from post market experience. Postmarket data were not included since the manufacturer did not recognise the need. This position is not acceptable since postmarket, 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, several 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[2]
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. The literature review of the peer-reviewed scientific literature uses keywords relevant for the subject. 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. CHIV transfusion transmissions have not been documented, and the potential for transfusion transmitted CHIKV infection is based on the transfusion transmissibility of other arboviruses, like DENV. DENV and CHIKV are most of the time asymptomatic, sometime with the same symptomatology. There are no documented cases of transfusion transmitted CHIKV and there are no standard guidelines regarding transfusion policies. We assume the medical value and public health benefit of the assay because transfusion transmission is probable, but we haven't got any evidence. It is supposed that asymptomatically infected persons can have high viral loads and are a substantial risk for transfusion transmission. To address potential risk for the EU reference is made two ECDC rapid risk assessments in 2017 on CHIKV because of outbreaks occurred in France and Italy. It is mentioned that "*These clusters of autochthonous cases led the ECDC to conclude preventative safety measures for donors residing in or returning from affected areas. Measures to prevent transmission of CHIKV through Substances of Human Origin (SoHO) include excluding blood or organ donations from travellers returning from affected areas, temporarily interrupting donations in affected areas in the absence of validated and authorized NAT for the screening of donors, and screening donors through NAT among other suggestions."* For DENV also 2 rapid risk assessments (2018, 2021) are referred to because of autochthonous transmission in France and Spain but also reports on the ECDC conclusion that: "*the likelihood of a dengue outbreak in mainland EU/EEA following introduction of the virus from Réunion was considered very low since environmental conditions do not favour vector activity and virus replication*", and "*…Although DENV can be transmitted through infectious SoHO, virus transmission risk cannot be*

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

assessed due to the small number of cases reported. Donation screening using NAT is the main tool to reduce the risk of transmission."

The manufacturer has thus provided an EU perspective but does not reflect on the true risk assessment in the EU region and does not include a benefit-risk assessment. It is recommended asking the manufacturer to reflect on this.

2. Expert views on the analytical performance report[3]

The analytical performance report gives a short overview of the analytical performance studies with reference to IVDR requirements. Reporting is tabular with only the main outcomes. For more details on e.g., 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. The summary report describes the technical performance verifications (TVPs), Assay Specific Analysis Package (ASAP) development and verification design transfer activities, and stability studies.

The TVPs included: Limit of Detection, Precision (Repeatability within Laboratory), Limit of Detection Verification of Genotypes/Serotypes, Genotype Inclusivity, Dilutional Sensitivity, Diagnostic Specificity, Matrix Equivalency, Endogenous Interference, Exogenous Interference, Cross reactivity (Analytical Specificity), Whole System failure, Correlation, Co-Infection Sensitivity, Clinical Specimen Stability, Lot Interchangeability, On Board and Open Kit Stability, RMC On Board Stability, IC/RMC Failure Rate and Sample Reliability.

The manufacturer's analytical performance report provides sufficient data for demonstration of the analytical performance of the device in relation to all parameters of the analytical performance. All data are available for making decisions if assay is appropriate for use from analytical point of view. Analytical performance well conducted for DENV and CHIKV (LoD for the 4 serotypes of DENV and the 3 genotypes of CHIKV). The IFU was well detailed, except for some information such as targets and pools (see below). 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.

In regard to inclusivity, due to clinical specimen unavailability of CHIKV East/Central/South African and CHIKV West African as well as limited specimen availability of DENV-3 (only 3 clinical specimens) the manufacturer has evaluated the inclusivity of the test using one cultured viral isolate of CHIKV East/Central/South African, and RNA of CHIKV from West African origin and an additional cultured viral isolate of DENV-3. However, RNA viruses have a high mutation rate*, as illustrated by changes in CHIKV and DENV sequences throughout the epidemics. These mutations can lead to false-negative results in clinical specimens when they occur in the annealing sites of the primers. So, to test a comprehensive inclusivity study the manufacturer should use known positive clinical samples.

*Drake JW, Holland JJ. Mutations rates among RNA viruses. Proc Natl Acad Sci 1999; 96 (24): 13910-3.
*Jenkins GM, Rambaut A, Pybus OG, Holmes EC. Rates of molecular evolution in RNA viruses: a quantitative phylogenetic analysis. J Mol Evol 2002;54 (2):156–65.

[3] Annex XIII, Section 1.2.2 of Regulation (EU) 2017/746 - Demonstration of the analytical performance

A number of observations were however, noted by the reviewers and are, if applicable discussed in the recommendations. These observations include:

- Information is missing about the target used for the detection, such as viral gene selected, which can be useful to evaluate the risk of variability over the different strains.
- No revision or postmarket use information since the first use (december 2017) is provided.
- There is no dertail about the number of samples which can be mixed (pool size) in the IFU, although the dossier mentions 1, 6 and 24 samples tested per pool
- The IFU mentions "the 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. " It should be clearly precise that the test is done on plasma (and not directly on the organs or tissues, so indirect testing).
- The limited panel of "clinical" samples, including only 1 artificial sample for West Africa CHIKV and 1 cultured isolate for ECSA CHIKV.
- The absence of data on any other alphaviruses (such as Venezuelian, Western etc.)
- Comparison with only one other NAT method

Regarding parameters that were omitted (limit of quantification, linearity, measuring range, 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[4]

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

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

The clinical performance report mentions that no clinicalal performance studies are conducted under IVDR.

Reproducibility was evaluated across 3 reagent lots, 5 days/lot, 2 batches/day), and within-batches (6 replicates/batch). The reproducibility goal was achieved for DENV but not for CHIKV due to the lot-to-lot variability observed for CHIKV at 1-time LOD.

The analytical sensitivity was tested with 5 different concentrations of well-characterized diluted standards of the target viruses. The results are not discussed in the clinical performance report. Reference is made to the report of the retrospective study.

These 2 clinical studies spiked samples only.

The clinical studies evaluated specificity in US blood donation center. No reactive donations for the 2 targets were found, with a prevalence of CHIKV/DENV reactive results of 0% (95% CI: 0% - 0.035%). Specificity for both CHIKV and DENV targets was 100% (95% CI: 99.97% - 100%), meeting the pre-defined acceptance criteria [redacted] for the lower limit of the 2-sided 95% CI.The other specificity study was conducted with blood specimens obtained from Puerto Rico. For both targets the overall specifity was 100% (95% Exact CI: 99.7% - 100%), meeting the pre-defined acceptance criteria of the lower bound of the 2-sided 95% [redacted] for both targets.

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

The manufacturer has not evaluated the diagnostic sensitivity of the assay in known positive samples, as is expected in a comprehensive clinical performance report. Two real clinical studies (retrospective) done on screening blood donors (Puerto Rico) and US. Tested with other NAT manufacturer, and hnPCR. But remains a specificity study only. No data are presented for pooled samples. The device is thereby suitable for its intended purpose and demonstrates its clinical utility, at least for single sample use. The clinical performance report is based upon historical data of studies prior to IVDR enactment.

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 DENV or CHIKV RNA in plasma samples to determine if blood products or tissues can be safely donated or transplanted into recipients. The device is a legacy device. There is no description on the development of the device since first introduction. Clinical performance data was gathered from different non-EU 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 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
Methodology for the literature search supporting the scientific validity is clearly and comprehensively described. For the intended purpose of the assay, the review on scientific validity is adequate. Literature comparing the manufacturers' assay and platform with other products on the market is missing. One publication tested clinical and spiked samples. No publications were found with less favourable or controverting findings, and no other published experience gained from routine diagnostic testing has been included. Although different publications on the detection of CHIKV and/or DENV in Asia are included, there are no publications of African genotypes of CHIVK, and no publication of American viruses. The literature review does not discuss virus variations. The assay under consideration has no significant innovations and has been in use in the market in Europe since December 2017. 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.

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 about the performance and safety of the device is in agreement with IVDR. Innovative aspect is moderate because company combined this assay with another diagnostic assay already in use.

The technology used, a nucleic acid test, (NAT) in plasma samples from human donors is a qualitative molecular method with CHIKV and DENV RNA target amplification by RT-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 donor 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 donor sample. Specific CHIKV, DENV and IC detection probes are labelled with one of four 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 blood donor screening.
Despite the technology is fit for purpose, as CHIKV and DENV have a high mutation rate, this can lead to false negative results if the mutations occur in the annealing sites of the primers/probes. Therefore "Principles of the Procedure" of the IFU should include which are the target genes of each virus [redacted] used.
Also, the manufacturer has developed in this assay a single region for each virus and this could lead to lack broad range coverage and make this method ineffective for a universal detection of CHIKV and DENV viruses. This assay would benefit of a double targeting in the genomic sequence of each virus.

Nucleic acid test technology has been used in blood donor screening to decrease the "window period" between initial infection and the antibody detection. The use of this technology is fit for purpose. These qualitative assays are widely used and generally accepted for screening. 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 state of the art technologies. The benefits of the product justify the overall residual risk acceptability. There have been no performance or safety concerns reported

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 sensitivity, specificity, reproducibility, and stability. The manufacturer has performed no additional clinical performance studies but has provided additional analytical studies with clinical samples and clinical studies to provide evidence as other sources of clinical performance data. These data also include retrospective analysis of data generated prior to the enactment of the IVDR.

The experts consider that the assay is a state-of-the-art product considering some factors.

First, the Clinical Performance Report describes the clinical evidence generated from a retrospective evaluation of analytical studies (including a range of performance characteristics such as LOD, genotype detection, specificity, correlation, cross reactivity, endogenous and exogenous interference, reproducibility and stability of samples and reagents), other sources of clinical performance data, and findings from scientific peer-reviewed literature that establish the overall clinical performance of the assay.

Secondly, the assay is adequate to design requirements and general safety and performance requirements, as documented in IVDR General Safety and Performance Requirements Checklist for IVD Reagent (DH-03226.04-198, pages 58-72).

Besides, the manufacturer has evaluated the performance of the product compared to other devices measuring the same analyte/marker and has shown evidence from the published scientific literature.

Finally, the Scientific Validity Report describes the state-of-the-art determination for the detection of CHIKV and DENV in donor samples and establishes that the device qualifies as state of the art in medicine.

In summary, the clinical evidence provided by the manufacturer was sufficient to determine suitability of the assay to safely be utilised for the intended use its intended use in blood donors screening populations.

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 believed this does not prevent final conclusions on the intended use, however, continued post market 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 different serotypes or genotypes. 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 specimens.

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 CHIKV/DENV 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, molecular screening of possible blood or tissue donor materials the submitted dossier provides analytical performance data in plasma sample and claims sensitivity and specificity in single samples as well as in pools. The latter are however not specified in the dossier or IFU. Particularly the IFU should be updated with this information.
2. Although the technology is fit for purpose, since CHIKV and DENV have a high mutation rate, this can lead to false negative results if the mutations occur in the annealing sites of the primers/probes. Therefore “Principles of the Procedure” of the IFU should include which are the target genes of each virus [redacted] are used.
3. The dossier does not include assay performance data in plasma from live tissue donor´s materials. The manufacturer is recommended to discuss the acceptability of extrapolating performance results from plasma pools to individual plasma samples.
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 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[5]
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[6], please summarise divergent positions
There were no divergent views

Please indicate how many of the experts of the panel had divergent views
TEXT

[5] 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.

[6] 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.