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	12/12/2023
Notified Body number	2797
Internal PECP dossier #	IVD-2023-000019
***In vitro* diagnostic medical device**	This test is intended for the screening of donor samples for the direct detection of *Plasmodium spp.* DNA and RNA in whole blood samples. It is also intended for use in testing whole blood samples to screen organ and tissue donors when samples are obtained while the donor's heart is still beating.

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)*	Plasmodium (P. *falciparum*, P. *malariae*, P. *vivax*, P. *ovale* and P. *knowlesi*) DNA and 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 the screening of donor samples for the direct detection of Plasmodium DNA and RNA in whole blood samples. It is also intended for use in testing whole blood samples to screen organ and tissue donors when 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.*	Malaria infection
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*	Whole blood

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.
P8	intended user	Trained laboratory professionals 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

2 VIEWS OF THE EXPERT PANEL

2.1 Information on panel and sub-group (where relevant)

Date of views	18/02/2024
Expert panel name	IVD expert panel
Sub-group of expert panel (where relevant)	IVD sub-group 2023-19

2.2 Summary of expert panel views

- **Device description:**

The device is a qualitative *in vitro* nucleic acid screening test for the direct detection of *Plasmodium* spp (*P. falciparum*, *P. malariae*, *P. vivax*, *P. ovale*, and *P. knowlesi*) DNA and RNA in whole blood samples from individual human donors or in pools of blood donor samples. The test is not intended for use as an aid in diagnosis of *Plasmodium* spp infection, on samples of cord blood or on cadaveric samples. The device technology is based on fully automated sample preparation (nucleic acid extraction and purification) followed by PCR amplification and detection.

- **Views on the performance evaluation report:**

The scientific validity, analytical performance, and clinical performance reports have enabled a qualified assessment of the performance of the device.

Scientific validity, including the generally acknowledged state of the art, was evaluated through comparison to devices measuring the same analyte/marker, scientific peer-reviewed literature that contains favorable and unfavorable publications, consensus from expert opinion/guidelines, results from clinical performance studies.

Analytical performance was assessed using technical performance verification studies. These study results demonstrate that the device is suitable for its intended purpose and detects the *Plasmodium* spp target with sufficient accuracy and precision.

Clinical performance was assessed using clinical performance studies and scientific peer-reviewed literature. These data demonstrate performance, safety, and efficacy and establish robust medical value for the product.

- **Views on the specific aspects of the performance evaluation report:**

The manufacturer's approach to gathering clinical evidence has addressed sufficiently the demonstration of scientific validity, analytical performance, and clinical performance. The manufacturer has carried out a review of the current scientific literature that validates the clinical performance of the device. The described technology, combining automated sample preparation with PCR amplification and detection, is in line with the current state of the art in molecular diagnostics.

The manufacturer has conducted a benefit-risk analysis to demonstrate that the benefit of the test for the safety of blood and organ/tissue donations, and the availability of supply for blood transmission and organ/tissue transplant to recipients in need, outweighs the residual risk.

The clinical evidence of the device against the state of the art in medicine has been described adequately and involves a comprehensive assessment of the device's clinical performance, technological innovation, and adherence to established standards.

- **Views on the adequacy of the approach chosen by the manufacturer:**

The overall risk associated with the assay reflects the state of the art, and the overall medical benefits of the product outweigh and justify the overall residual risk acceptability. The approach chosen by the manufacturer has been evaluated and is adequate to ensure the performance and safety of the device.

- **Overall conclusions and recommendations on the performance evaluation report:**

In summary, the experts are positive about the content of the submitted dossier. The information of the PER provided sufficient clinical evidence of scientific validity, analytical performance, clinical performance, and safety of the assay. The information provided supports the clinical benefit of the intended use. Recommendations are made throughout and at the end of this document.

2.3 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 Scientific Validity Report identifies relevant standards, clinical guidelines and best practices documents, and findings from the scientific peer-reviewed literature to demonstrate that the product meets the generally acknowledged state of the art in medicine. The manufacturer has summarized in the Scientific Validity Report the scientific background, peer-reviewed literature, and consensus expert opinions/positions from relevant professional associations to demonstrate that the device is a scientifically valid product. The device is consistent with the generally acknowledged state-of-the-art in medicine and technology for its intended purpose. The scientific validity has been evaluated through comparison to devices measuring the same analyte(s), scientific peer-reviewed literature containing favorable and unfavorable publications, consensus expert opinions or guidelines, and results from clinical performance studies and from other sources of clinical performance data. Devices measuring the same analyte(s): the manufacturer has compared the device to specifically commercially available CE-marked products, in order to demonstrate scientific validity. At the time of development of the device there were no commercial NAT devices for donor screening on the market. However, several sensitive NAT assays with “diagnostic” claim would have been available as suboptimal comparators. Some of these devices were even used for blood screening, despite the claim. In 2022, another manufacturer launched a test that detects *Plasmodium* spp RNA in donor samples for use in the blood screening market. Both tests appear to be similar with respect to their 95% limit of detection (LoD), to their use of an internal control and to detect all 5 clinically relevant *Plasmodium* spp (*P. falciparum, P. malariae, P. vivax, P. ovale,* and *P. knowlesi*), to comprise similar analytical specificity and clinical sensitivity.

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

Both assays appear to meet the generally acknowledged state of the art for *Plasmodium* spp donor screening, both for pooled and individual donor samples.

Scientific peer-reviewed literature: the manufacturer has reviewed the current scientific literature and demonstrated the scientific validity of NAT testing for malaria. Literature searches have been performed across multiple databases using a literature search protocol, and a literature search report has been summarized within this document.

Consensus expert opinions/positions from relevant professional associations: the manufacturer has provided clinical guidelines and expert opinions from professional organizations and societies, with a particular focus on European guidelines. The European Centre for Disease Prevention and Control (ECDC) recommends that vigilance should remain high with regard to malaria transmission through substances of human origin (e.g., blood products or organ transplants). The Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) recommends discretionary testing for malaria in some cases. The Council of Europe and the U.S. Food and Drug Administration (FDA) have similar recommendations. The World Health Organization (WHO) guidelines for reducing transfusion-transmitted malaria (TTM) in endemic countries include testing of donors by microscopy or antigen, but recent studies have established the higher sensitivity of molecular testing compared to these methods and suggest the potential utility of NAT in donor screening.

Results from clinical performance studies: clinical performance studies were performed to evaluate the device for the detection of *Plasmodium* spp DNA and RNA from blood donors. Results from these performance studies are summarized in the Clinical Performance Report. There are no other sources of clinical performance data for the device.

In conclusion, the scientific validity of NAT testing for malaria has been established by evidence from scientific peer-reviewed literature. The manufacturer has conducted diagnostic evaluations to support the safety, effectiveness, and scientific validity of the device. Collectively, the technical performance verification and clinical studies demonstrate that the product is consistent with the generally acknowledged state of the art for its intended purpose, the scientific validity of the product, and that the medical value and public health benefit outweigh the potential risks of the product. Clinical studies demonstrate the clinical performance of the device and support its intended purpose for detection of *Plasmodium* spp DNA and RNA in samples from human donors to fulfill the requirements of the IVDR.

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

The manufacturer has made several technical performance verification (TPV) studies in order to show acceptable performance of the device and that it is suitable for its intended purpose. The analytical report assessed the following analytical parameters:

i. Limit of detection (LoD) or analytical sensitivity: the manufacturer has carried out three dilution series of 5 levels plus a blank which were tested across three reagent lots, three days, two runs per day, three operators, three systems and 22 replicates per level, per lot. The LoD for *Plasmodium falciparum* based on Probit Analysis is 0.058 infected red blood cell (iRBC)/mL of whole blood using a pre-lysed in-house standard (95% CI: 0.049-0.071 iRBC/mL). The LoD for *Plasmodium knowlesi* is 0.044 iRBC/mL (95% CI: 0.037-0.054 iRBC/mL). And the LoD for *Plasmodium vivax* is 0.012 iRBC/mL (95% CI: 0.010-0.015 iRBC/mL). In summary, the device can detect the target nucleic acids from less than 1 infected red blood cell per ml, meeting the pre-defined acceptance criteria.

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

The manufacturer also has carried out a study to determine the LoD of the device using armored RNA in generic specimen diluent. Despite there were no specific acceptance criteria for this study, the resulting LoD for the five *Plasmodium* spp (*P. falciparum, P. vivax*, *P. knowlesi*, *P.* m*alariae* and *P. ovale*) were suitable, being in a range from 23.7 to 59 RNA particles/ml.

Finally, the manufacturer has performed a study to evaluate the dilutional sensitivity of the device, testing serial dilutions of positive clinical specimens from individuals infected with *Plasmodium falciparum* and with *Plasmodium vivax.* The reactive rates vary from 94,6% (1xLoD) to 100% (3xLoD) for *P. falciparum* and 92,5% (1xLoD) to 99,6% (3xLoD) for *P. vivax*. These rates are suitable for screening studies. As the study doesn't include the other species (*P. malariae, P. ovale* and *P. knowlesi*), although the device has been developed to detect all species, this should be considered in post-market surveillance activities.

Metrological traceability to standards of higher order was not evaluated despite establishment of a World Health Organization International Standard for *Plasmodium falciparum* DNA. The manufacturer argues that this reference material has been value assigned (International Units) for *Plasmodium* spp DNA exclusively, not *Plasmodium* spp RNA, while the assay detects both nucleic acid types. Although the rationale can be followed, we think it is important to demonstrate with the use of such international reference materials an analytical sensitivity which is at least equivalent to the analytical sensitivity exhibited by comparator assays which amplify only one of these nucleic acid types.

ii. Clinical specificity: the manufacturer has tested 500 negative whole blood specimens from healthy donors collected in a non-endemic region resulting in a specificity of 100.0%.

iii. Inclusivity: the manufacturer has developed a study to demonstrate the detection of all five claimed *Plasmodium* spp (*P. falciparum, P. vivax, P. malariae, P. ovale* and *P. knowlesi*). All positive specimens for each species were detected when tested neat (*P. falciparum, P. vivax, P. malariae* and *P. ovale*) and at 3xLoD (*P. falciparum, P. vivax, P. malariae, P. ovale* and *P. knowlesi*), showing reactive rates of 100%.

iv. Cross reactivity or analytical specificity: the manufacturer has performed a cross-reactivity study to evaluate potential interference with other microorganisms that may cause infectious diseases. Six different viruses, 8 different bacteria, 1 parasite, and 1 yeast were spiked at different concentrations and tested in triplicate with both unspiked and spiked specimens with malaria target at 3x LoD. No cross-reaction was observed in all the samples with potential cross-reactants.

v. Endogenous and exogenous interference: no interference was observed with different classical endogenous substances, such as albumin, bilirubin, hemoglobin (≥ 20 g/dL), human DNA and triglycerides. In the same way, the manufacturer has evaluated the influence of potentially interfering exogenous substances, such as acetaminophen, acetylsalicylic acid, atorvastatin, atovaquone, azithromycin, fluoxetine, loratadine, atenolol, naproxen, paroxetine, sertraline, ascorbic acid (vitamin C), ibuprofen and phenylephrine HCl. The specificity and sensitivity of the device were not affected by the potential exogenous interferents tested.

vi. Cut-off: determining a cut-off in a screening test involves a careful analysis of various factors related to the specific test and the condition being screened, and the manufacturer is expected to perform a Receiver Operating Characteristic (ROC) analysis, so the area under the ROC curve (AUC) can help to identify an optimal cut-off that balances sensitivity and specificity. However, the manufacturer argues that the cut-off criteria are based in multiple parameters (such as the Cycle Threshold and the Relative Fluorescence Intensity) which are considered collectively and set on the experience of algorithm developers. Data from ongoing product development is continuously reviewed, and the algorithm is refined based on the experience and insights gained from the analysis of this data. Overall, the manufacturer describes a dynamic and iterative approach to developing and refining the algorithm

used in the device, taking into account multiple parameters to enhance the accuracy of result interpretation. In summary, the method described appears to be a thoughtful and systematic way to determine cut-off criteria for a screening test. The multifactorial approach is a robust approach, the iterative process provides strength, and expert annotation adds credibility to the process. However, the effectiveness of this method also depends on the specific characteristics of the disease or condition being screened, the nature of the test, and the quality and representativeness of the data used for iterative adjustments. Regular validation studies and ongoing monitoring are crucial to ensuring the performance of the screening test over time.

vii. Repeatability or precision: the manufacturer has studied the repeatability (precision) of the device within Day-to-Day, Operator-to-Operator, Reagent Lot-to-Lot, Instrument-to-Instrument and Run-to-Run variation for *P. falciparum*, *P. knowlesi*, and *P. vivax*. Overall, the device demonstrated repeatable over multiple days, reagent lots, runs, instruments, and operators for each *Plasmodium* spp tested.

viii. Specimen stability: specimen handling, collection, and storage are critically important as they can significantly impact the accuracy and reliability of test results. Two studies conducted to determine the clinical specimen stability under various storage conditions and time periods show acceptable results, and samples can be stored under different conditions.

ix. Kit lot interchangeability: these studies are conducted to assess whether different lots of the same test kit can be used interchangeably without compromising the test's accuracy and reliability of the screening test. The manufacturer has carried out this study testing 3 lot combinations of reagents. The results of the study indicate that different lots of test specific reagents and controls can be used interchangeably. The study is well-conducted and supports the use of different lots interchangeably and enhances the overall value and reliability of the screening test. Besides, it indicates that the manufacturer has a robust and reproducible manufacturing process.

x. Robustness: a study to determine the rate of Whole System Failure or robustness has been performed. This kind of study, specifically focusing on failures leading to false negative results, is critically important in evaluating the performance and reliability of a diagnostic device. The Whole System Failure rate observed in this study was 0%. The manufacturer has carried out a thorough assessment of the whole system, including potential failure points that lead to false negatives, and contributing to the overall quality assurance of the diagnostic test. However, it is important to notice that the manufacturer has not provided data about the potential carry-over of the technology. The Common Specifications for other class D pathogens request, for their respective NAT assays, at least five runs with alternating high-positive and negative specimens, with high positive specimens representing pathogen concentrations occurring naturally."

xi. Failure rates: the manufacturer has evaluated the failure rates of the internal control, external controls and the sample reliability by analyzing data generated from multiple technical performance verification studies. The control failure rate was ≤ 1% and the sample reliability was >99%. However, the combined results from technical performance verification (TPV) studies and Specificity clinical trial data did not meet the predefined acceptance criteria of Internal Control Failure Rate at ≤ 0.5%. Despite not meeting the requirement, a decision was made to proceed with the implementation of the device. This suggests that, despite the higher IC Failure Rate, the overall assessment concluded that the risk is acceptable from both a medical and business perspective.

xii. Diagnostic specificity: the manufacturer has developed a study to assess the assay performance equivalency between two different systems regarding diagnostic specificity. The overall percentage agreement was 100% with a lower bound of one-sided 97.5% confidence interval of 99.3%.

There are some required studies that were not conducted by the manufacturer. The device is a qualitative test and only reports the presence or absence of the test target. Since the reported result is not quantitative

in nature, studies to determine analytical performance for limit of quantitation, measuring range, and linearity were not conducted. Regarding the accuracy of measurement or trueness, the manufacturer argues that at the time of development of the device, there were no certified reference materials or methods available, and that is the reason why studies to determine analytical performance for trueness were not conducted.

The performance report provides analytical and clinical performance data. Risk assessment has been documented properly. Analytical performance has been investigated and documented for *P. falciparum*, *P. knowlesi*, and *P. vivax*.

In conclusion, and based on the results of the studies, analytical performance data demonstrates the state-of-the-art performance of the assay and met all the analytical requirements detailed above, demonstrating that the test is suitable for its intended purpose and detects the DNA and RNA of the causative agents of malaria with sufficient accuracy and precision in whole blood samples from individual human donors.

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

Clinical performance parameters were determined based on the intended purpose of the device. The manufacturer has provided a Clinical Performance Plan and Clinical Validation Plan which describes the planned clinical assessment of the test and includes a review of medically relevant studies designed to assess product suitability in medical decision making, as well as studies designed to validate the clinical performance of the product.

The clinical performance of a screening test should assess its accuracy and reliability in real-world clinical settings, considering patient samples and the intended use of the test. In this context, the manufacturer has developed a Clinical Performance Report (CPR) in order to provide a summary of the clinical and analytical performance data, evidence from the scientific peer-reviewed literature and to demonstrate that the device meets the clinical performance requirements as stated in the *in vitro* Diagnostic Regulation (IVDR) for its intended use. Clinical performance studies conducted have generated substantial and relevant data that validate the performance, safety, and efficacy for the product.

The following performance characteristics were included in the Clinical Performance Report: medical value assessment, comparator devices measuring the same analyte, the intended use of the device, analytical performance studies, clinical performance studies, scientific peer-reviewed literature and published experience gained from routine diagnostic testing.

Analytical and clinical performance studies indicate that the device has robust medical value for the detection in the intended use population. In regard to analytical performance studies, a medical review of analytical performance or TPV studies designed to assess test suitability and product performance supports the medical value of the test. The results of the available data have been compared against the product's intended use and proposed medical value.

Regarding the clinical performance studies, the manufacturer has carried out three clinical studies: reproducibility, sensitivity and specificity.

- Reproducibility: the objective of this study was to evaluate the reproducibility of the device across lot, site/system, day, and batch and within-batch. Reproducibility was established for the test for all 5 *Plasmodium* spp known to cause human disease, *P. falciparum*, *P. knowlesi*, *P. malariae*, *P. ovale*, and *P. vivax*, across the 5 parameters mentioned above. These results show that the device provides high reliability for use to screen the blood supply for the presence of these *Plasmodium* spp RNA and DNA.

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

- Sensitivity: the objective of this study was to evaluate the performance of the device on confirmed *Plasmodium* NAT-positive samples. Sensitivity was evaluated using 417 samples (clinical and contrived) known to be positive for *Plasmodium* spp by NAT testing. Overall, the device showed 100% overall reactivity in clinical and contrived Plasmodium-positive samples in neat whole blood-PCR media samples and 99.8% in diluted (1:6) samples. The device was able to detect effectively any of the 5 *Plasmodium* spp known to cause human disease, if present in a blood donation, and provides additional, high-sensitivity protection for the safety of the blood supply.
- Specificity: the objective of this clinical study was to evaluate the specificity of the device with blood samples collected from donors of whole blood or blood products. A total of 88,021 whole blood donations were collected from donors included in this study; 20.288 were tested initially individually and 67.733 were tested in whole blood primary pools of 6. The device demonstrated excellent overall clinical specificity in both individually (100%; 20,187/20,187; 95% exact CI: 99.982% to 100%) and pooled screening (100%; 67,612/67,612; 95% exact CI: 99.995% to 100%). These results support the proposed intended use of the device, a qualitative in vitro NAT for the detection of *Plasmodium* spp. RNA and DNA in donor whole blood samples when tested individually or pooled. The test will provide additional protection of the blood supply from any of the 5 *Plasmodium* spp known to cause human disease. This study should have been performed with a comparator screening NAT device for exclusion of potential false-negative results.
- Positive Predictive Value (PPV) and Negative Predictive Value (NPV) are important metrics in the evaluation of diagnostic and screening tests. These values provide insights into the reliability and accuracy of the test in real-world scenarios and are particularly useful in understanding the implications of test results in particular populations. No appropriate comparator assay was included and PPV and NPV were not calculated by the manufacturer. Nevertheless, it is estimated that including PPV and NPV in the Clinical Performance Report is beneficial because they provide a more comprehensive picture of a test's performance by considering the prevalence of the condition in the population being tested.
- Comparison with other tests: the manufacturer has compared the detection of malaria infection by the device with detection by an antibody test, as well as locally available microscopy and antigen tests, in healthy individuals in malaria-endemic regions. Again, appropriate comparator NAT assay is missing. The positive percent agreement was 100% (4/4; 95% CI: 51.0% to 100%). The data showed that the device is an effective and reliable method to detect the presence of *Plasmodium* spp nucleic acid in blood samples from healthy adults in a region where malaria is endemic.

Finally, in regard to the Scientific Peer-Reviewed Literature, literature searches have been performed across multiple databases using a literature search protocol and no published literature was identified for the clinical performance of the device. No other relevant published experience gained from routine diagnostic testing is provided in this document for the clinical performance of the device, although there are several conference abstracts about the clinical performance of another assay measuring the same analyte.

Clinical performance report data have been provided in detail and show adequate clinical performance of the device submitted. The result of the clinical sensitivity report has been provided additionally, providing limit of detection data. The aim of the studies was to prove that transfusion-transmitted malaria can be prevented by the new device. To do so, negative and positive samples have been analyzed by direct detection of *Plasmodium* spp DNA and RNA. The report revealed a very good sensitivity and specificity of the test. Malaria Technical Performance Verification Study Report using clinical specimens reveals a 100 % specificity.

In conclusion, the Clinical Performance Report demonstrates the clinical performance of the device, and it has been based on clinical performance studies. These clinical performance studies conducted have generated substantial and relevant data that validate the performance of the device and establish robust medical value for the detection of *Plasmodium* spp DNA and RNA in the intended population. These clinical performance studies in combination with the scientific peer-reviewed literature support compliance with the requirements. Additionally, evidence from supporting publications, including original and review journal articles and recommended clinical guidelines obtained from a thorough review of the literature, further support the utility of a *Plasmodium* spp NAT for use in blood screening. The device is a novel test, so no publications were found regarding its use.

2.4 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
The manufacturer's approach to gather clinical evidence has addressed sufficiently the demonstration of scientific validity, analytical performance, and clinical performance. The manufacturer has provided a Clinical Performance Plan and Clinical Validation Plan of the device to define the requirements and activities to determine the clinical evidence that supports the intended use to demonstrate conformity with the relevant general safety and performance requirements. The assessment has included a review of medically relevant technical performance verification studies and analytical performance studies designed to assess product suitability in medical decision-making, as well as clinical studies designed to validate the clinical performance of the product. The plan ensures that the device is fit for clinical purposes and that the clinical performance meets the certification requirements. The manufacturer has carried out a medical value assessment and has provided a summary of medical decisions points and medical risks. The scientific validity, analytical performance, and clinical performance reports have enabled a qualified assessment of the performance of the device. Scientific validity, including the generally acknowledged state of the art, has been evaluated through comparison to devices measuring the same analyte/marker, scientific peer-reviewed literature that contains favourable and unfavourable publications, consensus from expert opinion/guidelines and results from clinical performance studies. Analytical performance has been assessed using technical performance verification studies that demonstrate that the device is suitable for its intended purpose and detects the *Plasmodium* spp target with sufficient accuracy and precision. Finally, clinical performance has been assessed using clinical performance studies and scientific peer-reviewed literature. These data demonstrate performance, safety, and efficacy and establish robust medical value for the product. The provided documents indicate a good sensitivity and specificity of the novel device. This is relevant to prevent providing *Plasmodium* spp contaminated blood samples. Information provided about specificity is relevant to exclude unnecessary loss of blood products. The justification of the manufacturer is agreed.
2. The literature search methodology, protocol and report

The manufacturer has carried out a review of the current scientific literature that validates the clinical performance of the device. The literature search methodology used to assess the nature and extent of scientific validity, including a "literature search protocol" and "literature search report" have been documented by the manufacturer.

Scientific validity of the product has been investigated in scientific peer-reviewed literature. Conclusion provides evidence for the chosen approach. Malaria infections are a world-wide challenge. Due to motility and climate changes, positive samples have to be expected everywhere and must be excluded from blood products.

The search has been conducted using databases like PubMed, ProQuest/Dialog and Wiley Online Library. Given that PubMed is specifically focused on biomedicine and life sciences, its use is particularly relevant for a clinical performance report in the context of a medical diagnostic device. The use of ProQuest/Dialog suggests a broader search strategy, possibly including multidisciplinary sources beyond biomedicine. Finally, the use of Wiley Online Library suggests that the manufacturer has conducted a thorough and comprehensive literature search, including a diverse range of sources. When a manufacturer uses these databases in the context of a clinical performance report, it indicates a systematic and comprehensive approach to gathering relevant literature to support the clinical performance claims of their diagnostic device.

The literature search methodology and literature search protocol are suitable and includes search terms queried, date range (2012-2023) and the number of publications retrieved. Relevance of literature has been assessed using adequate inclusion and exclusion criteria. The manufacturer selects appropriate keywords and relevant databases using Boolean operators (e.g., AND, OR, NOT) to combine keywords and refine search queries. Search results were screened for relevance, quality, and performance outcomes, and eligible articles have been included in the report.

Regarding the literature search report, the manufacturer has summarized in this document the relevant publications that demonstrate the potential value of malaria NAT screening. NAT tests that screen donor samples for the presence of *Plasmodium* spp RNA or DNA are relatively new and the published scientific literature about performance or utility of *Plasmodium* spp screening tests is quite limited. Only two articles were retrieved: the first is an original article from 2020, in which authors evaluated NAT screening for malaria for the prevention of transfusion-transmitted malaria in Brazil; the second is a systematic review from 2019 which summarizes the prevalence of *Plasmodium* spp infections in asymptomatic blood donors and the effectiveness of screening methods.

Relevant scientific literature was screened extensively, and publications with less favorable or controverting findings were not found. This is the expected outcome as this assay is currently under development. Finally, no other published experience gained from routine diagnostic testing exists for the device.

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 device technology is based on fully automated sample preparation (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 Plasmodium nucleic acid provide a selective amplification of targets from the donor sample. The master mix contains detection probes which are specific for *Plasmodium* spp and internal control nucleic acid which are each labeled with one of two unique fluorescent dyes which act as a reporter. The reporter dyes are measured at a defined wavelength, thus permitting detection and

discrimination of the amplified *Plasmodium* spp targets and the IC. With each PCR cycle, increasing amounts of cleaved probes are generated and the cumulative signal of the reporter dyes are concomitantly increased. Since the two specific reporter dyes are measured at defined wavelengths, simultaneous detection and discrimination of the amplified *Plasmodium* spp targets and the IC are possible.

The use of this technology is fit for purpose. The use of fully automated sample preparation followed by PCR amplification and detection is a common and well-established approach in molecular diagnostics. This process combines nucleic acid extraction, purification, and amplification in a streamlined and efficient manner. Automation reduces the risk of human error, enhances reproducibility, and increases throughput, making the testing process more efficient. Fully automated sample preparation is considered state-of-the-art in molecular diagnostics, improving the reliability and consistency of results. Automated detection methods, such as real-time PCR in particular, are a widely adopted and state-of-the-art technique for nucleic acid detection. Furthermore, inclusion of an Uracil-N-Glycosylase (UNG) step prevents potential contamination by degrading amplicons from previous reactions, otherwise potentially serving as target nucleic acids.

The device is based on real-time PCR detection of both DNA and RNA in parallel without further differentiation. Relation between specific RNA and DNA and potential consequences for diagnostics performance are not part of the PER. Technical and diagnostic performance of parallel detection of the two types of nucleic acids are expected to be superior compared to exclusive DNA or RNA detection, nevertheless, the scientific background for choosing this approach is expected to be communicated to the user. A respective data-based explanation in the IFU is missing.

In conclusion, the described technology, combining automated sample preparation with PCR amplification and detection, is in line with the current state of the art in molecular diagnostics. Automated sample preparation, coupled with PCR amplification, detection and subsequent amplicon degradation represents a robust and efficient approach for screening tests and contributes to the overall efficiency, accuracy, and reproducibility of the test.

In regard to the intended purpose of the device, the manufacturer has provided a document with a description of the intended use and features. The test is a qualitative *in vitro* nucleic acid screening test for the direct detection of *Plasmodium* spp *(P. falciparum, P. malariae, P. vivax, P. ovale,* and *P. knowlesi)* DNA and RNA in whole blood samples from individual human donors, including donors of whole blood and blood components, as well as other living donors. It is also intended for use in testing whole blood samples to screen organ and tissue donors when samples are obtained while the donor's heart is still beating. The test is not intended for use as an aid in diagnosis of *Plasmodium* spp infection, on samples of cord blood or on cadaveric samples.

With regard to the device's safety and performance characteristics, they are based on the intended purpose of the device and are maintained throughout the product lifecycle. The Risk Management Report summarizes the results of the risk management activities conducted for the device according to the Risk Management Plan, but this plan has not been provided by the manufacturer. The report also provides a summary of the risk management activities, identified product risks, and implemented mitigations for the test**.** The identified risks include those associated with product safety, performance, and the environment.

The manufacturer has reduced the risk level as far as possible for each risk consistent with the benefit/risk ratio and the state of the art for the product. This report shows that each of the residual risk levels is acceptable and there were no intolerable risks identified, although the exact justification is not provided.

The manufacturer also has provided an identification of the general safety and performance requirements (GSPR) of the device. The checklist provides a cross-reference between the IVDR requirements and activities

conducted throughout the life of the product, including the scientific validity and the analytical and clinical performance data.

In conclusion, the manufacturer has conducted a benefit-risk analysis to demonstrate that the benefit of the test for the safety of blood and organ/tissue donations, and the availability of supply for blood transmission and organ/tissue transplant to recipients in need, outweighs the residual risk. The overall risk associated with the device is comparable to the state of the art, and the overall benefits of the product justify the overall risk acceptability.

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

The clinical evidence of the device against the state of the art in medicine has been described adequately and involves a comprehensive assessment of the device's clinical performance, technological innovation, and adherence to established standards. The manufacturer has ensured that the device is not only accurate and reliable but also aligns with current best practices and expectations within the medical community. This is crucial for determining the reliability and relevance of the device in a clinical setting.

The clinical data generated by the device are clinically relevant and meaningful for the intended use. The manufacturer has evaluated the device's accuracy and precision, the robustness of the device's performance across different sample types, conditions, and patient populations. The device's technology and methodology has been compared to the current state of the art in screening tools for specific medical conditions. Finally, the device's clinical evidence aligns with established clinical standards and guidelines and the device has been validated in diverse clinical settings and patient populations to ensure its applicability across a range of scenarios.

The provided documents indicate a good sensitivity and specificity of the novel device. The intended use of the product is restricted to blood safety in blood banking.

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

The manufacturer has not provided a Post-Market Performance Follow-up Report and justifies that it is not necessary at this time because it is a novel product and will advance the state of the art for malaria blood donor screening. The manufacturer argues that "*the product is subject to continuous post-market monitoring, including complaint and complaint trend evaluation, monitoring for publications in the scientific literature, and frequent interactions with customers and key opinion leaders. This process ensures that the safety and performance are continuously evaluated throughout the product lifetime and that emerging risks that could affect performance, including risks created due to foreseeable misuse, are identified, at which point, the need for PMPF may be re-evaluated*".

It is this Expert Panel's opinion that a comprehensive post-market performance follow-up report, when available, will be crucial for maintaining the quality and safety of a device screening DNA and RNA of *Plasmodium* spp in human blood donors. This report will be a valuable tool for the manufacturer, regulatory authorities, and healthcare professionals to ensure that the device continues to meet or exceed expectations in real-world use.

The current status of the post-market surveillance should be summarized: post-market surveillance plan in place, frequency and scope of post-market surveillance activities, monitoring of adverse events and safety issues related to the device and whether there have been any reports, updates or modifications to the device, or its labeling based on post-market surveillance findings, collection of feedback from users (user satisfaction or concerns).

2.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report
The information of the PER provided sufficient clinical evidence of scientific validity, analytical performance, clinical performance, and safety of the assay. Information provided supports the clinical benefit of the intended use. Points to be considered by the manufacturer (in addition to other comments) are: (1) Use of international reference preparations for sensitivity characterization of the device relative to comparator device(s), even if unitage assignment does not cover all nucleic acid types (3.3.2.). (2) Comparative evaluations using sensitive NAT devices (even with exclusive "diagnostic" claim) as comparator devices, in the absence of suitable comparator screening devices (3.3.1., 3.3.3.). (3) References to European requirements on malaria safety in the Instruction for Use (IFU), e.g. as defined by the human blood and blood components Directive or by EU Member States. (4) In the IFU of the European version of the device, the maximal pool size for blood donor specimens is not defined which is agreed; however, it should be mentioned that a pool size of 6 has been validated by the manufacturer. (5) The scientific rationale for the assay design with co-detection of *Plasmodium* spp DNA and RNA should be communicated in the IFU, together with a summary of respective data.

2.6 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[4]
Has the Secretariat provided information from stakeholders?
☐ YES ☒ NO

2.7 Divergent positions in case no consensus can be reached

In case no consensus on the views can be achieved[5], please indicate how many of the experts of the panel had divergent positions
No divergent positions.
Please summarise those divergent positions, if applicable
N/A.

[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.