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	30/11/2021
Notified Body number	0123
Internal PECP dossier #	IVD-2021-000015
***In vitro* diagnostic medical device**	Chemiluminescent microparticle immunoassay (CMIA) used for the qualitative detection of antibodies to *Treponema pallidum* in human serum and plasma, including specimens collected post-mortem (non-heart-beating) using propietary instrumentation.

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)*	Antibodies to Treponema pallidum
P2	function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc*	• Aid in the diagnosis of Syphilis infection • As a screening test to prevent transmission of Treponema pallidum to recipients of blood, blood components, cells, tissues, and organs
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.*	Syphilis
P4	whether it is automated or not	Automated
P5	whether it is qualitative, semi-quantitative or quantitative	Qualitative
P6	type of specimen(s)	• Human Serum and Plasma • Serum and Plasma specimens from Cadaveric (non-heart beating) donors

	e.g. whole blood, serum, saliva etc	
P7	where applicable, the testing population *e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range*	• Volunteer blood donors of whole blood and blood components • Organ donors when specimens are obtained while the donor's heart is still beating • Cadaveric (non-heart-beating) donors • Individuals suspected to have syphilis infection
P8	intended user	For Laboratory Professional Use Only
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.*	Chemiluminescent microparticle immunoassay (CMIA) technology

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group

Date of views	03/02/2022
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-15

3.2 Summary of expert panel views

The device is intended for the qualitative detection of *Treponema pallidum* antibodies (IgG and IgM) to syphilis in human serum or plasma collected from donors (including specimens collected post-mortem) with the intended purposes of screening in blood banks and plasma centres to prevent transfusion transmitted infection and as an aid to diagnosis of syphilis in clinical laboratories. The technology is based on a chemiluminescent microparticle immunoassay (CMIA) that runs on a dedicated high-throughput fully-automated analyser and is intended for laboratory professional use only. The principle of the CMIA relies on binding of *Treponema pallidum* antibodies to recombinant *Treponema pallidum* antigen-coated microparticles and measurement of the value of the resulting chemiluminescent reaction compared to a cut-off value determined from calibration. The CMIA includes a reagent kit for use in combination with other separate components (a calibrator kit, a control kit, and a release control kit) that are each classified as Class D products.

- ***Views on the performance evaluation report:*** *please provide a short summary of the expert views on a) the scientific validity report, b) the analytical performance report and c) the clinical performance report (see section 3.3).*

The scientific validity report provided adequate background on *Treponema pallidum* as the causal pathogen of syphilis as well as background on the successive stages of syphilis infection and on the different testing approaches and diagnostic algorithms recommended by significant public health institutions, including ECDC, CDC, and WHO. Evidence contained in the report was sufficient to support the suitability of using a device based on the detection of *Treponema pallidum* antibodies as an aid in the diagnosis of syphilis infection and for screening to prevent the transmission of *Treponema pallidum* to recipients of blood, blood component, cells, tissues, and organs.

The analytical performance report assessed all relevant parameters required for qualitative detection of *Treponema pallidum* antibodies, except for the Limit of Detection (LoD). The justification of the manufacturer for omitting the specification of the LoD, based on the unavailability of NIBSC Code 05/132 WHO standard from the vendor and the fact that the device delivers qualitative results, is considered a shortcoming. LoD is an important parameter of performance that must be determined for both quantitative and qualitative assays, as stated by accredited standards (i.e. the Clinical Laboratory Standards Institute CLSI EP17 protocol). Positive samples were used for stability. For sample type studies spiked samples rather than true patient samples were used. The extent of evaluation for the rest of analytical parameters was appropriate, including the use of a sufficient number of samples or replicates, the definition of suitable acceptance criteria for analytical performance parameters, the conduct of adequate data analysis, and the reporting of acceptable values of performance.

The clinical performance report evaluated the performance of the device appropriately under the intended conditions of use for screening of syphilis among blood donors and as an aid to syphilis diagnosis. All clinical performance parameters were assessed using a sufficient number of negative samples as well as a sufficient number of positive clinical samples across the diverse stages of syphilis infection. Selected positive samples were representative of all the different stages of syphilis infection. Negative samples were randomly selected. Reference assays used for comparative clinical performance were adequate according to state of the art. Acceptance criteria for values of clinical performance parameters were well defined, and values reported for clinical sensitivity and clinical specificity were optimal. Although the manufacturer included a well-designed PMPF in the PER, a PMPF report was not available for assessment of device safety.

- ***Views on the specific aspects of the performance evaluation report*****:** *please provide a short summary of the expert views on the specific aspects of the PER: manufacturer's justification for the approach to gather the clinical evidence; literature search methodology, protocol and report, including the adequacy of the literature review; appropriateness of technology to reach the intended purpose and the manufacturer's claims about the performance and safety; acceptability of clinical evidence(see section 3.4). Where applicable, please provide your views on any innovative aspects, especially the technology on which the device is based and/or the intended purpose.*

The manufacturer gathered clinical evidence in sufficient amount and quality to support the device claims. The literature search method described to conduct the literature review was thorough and various sources of information were consulted including those of relevant public health institutions

(ECDC, CDC, WHO). The use of commercially sourced positive clinical samples allowed demonstrating clinical sensitivity for screening was an appropriate approach to circumvent the potential problem of low prevalence of syphilis among donors. The technology on which the CMIA device is based is a well-known serological method that has been routinely used for screening and as an aid to diagnosis of syphilis in many developed countries over the last years. Reported values for analytical and clinical performance parameters were calculated with sufficient statistical validity and are acceptable for the intended uses of the device. Although the manufacturer included a well-designed PMPF in the PER, a PMPF report was not available for assessment of device safety.

- ***Views on the adequacy of the approach chosen by the manufacturer*** *(in the absence of CS) to evaluate and ensure performance and safety of the device*

In general, evaluation of analytical and clinical performance parameters was appropriate, including the use of a sufficient number of samples or replicates, the definition of suitable acceptance criteria for values of analytical and clinical performance, the selection of appropriate reference methods for clinical performance comparison, the conduct of adequate data analysis, and the reporting of acceptable values of performance. Consideration of draft CS and CLSI guidance was noted in the design of the studies. However, some shortcomings were identified: the LoD was not determined and the unavailability of a PMPF report did not allow assessing device safety.

- ***Overall conclusions and recommendations on the performance evaluation report:*** *please summarise pertinent conclusions and provide recommendations where applicable (see section 3.5).*

In general, the information of the PER provided sufficient clinical evidence of scientific validity, analytical performance, clinical performance. Data reported support the clinical benefit of using the device for the intended purposes. It is recommendable that the manufacturer be requested to provide further information regarding:

i) The device LoD.
ii) The PMPF report and data of device safety in operational conditions.

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

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

Views of the expert panel on the performance evaluation report of the manufacturer (PER)
1. Expert views on the scientific validity report[1]
The scientific validity report provided adequate background on *Treponema pallidum* as the causal pathogen of syphilis as well as background on the successive stages of syphilis infection and on the different testing approaches and diagnostic algorithms recommended by significant public health institutions, including the ECDC. Relevant data were collected from different sources of information

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

including: i) accredited data bases of scientific publications (16 references); ii) WHO and CDC public health institutions (7 references); and iii) literature identified through an adequate search strategy and selection criteria (6 references selected out of 52 references initially screened). Evidence contained in the report was sufficient to support the suitability of using a device based on the detection of *Treponema pallidum* antibodies as an aid in the diagnosis of syphilis infection and for screening to prevent the transmission of *Treponema pallidum* to recipients of blood, blood component, cells, tissues and organs.

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

The analytical report assessed diverse analytical parameters, including among others:

i) Analytical specificity. A panel of 288 potentially cross-reacting samples from individuals with medical conditions unrelated to *Treponema pallidum* infection were assessed and 10 of them were repeatedly reactive.
ii) Analytical interference. Diverse potential interfering substances were tested, and their interfering levels were determined.
iii) Precision (repeatability). Low- and high-positive samples were used for assessment over 20 consecutive days for a minimum of 320 measurements. Reported CV values were in the range 4.3-5.1% for low-positive samples and 4.1-4.5% for high-positive samples.
iv) Precision (reproducibility). Evaluation was conducted in two external sites, considering within-run, between-run, between-site, and between-day variability across 5 days for a minimum of 360 measurements. Reported CV values were 5.4% and 6.1% for low- and high-positive samples, respectively. However, surprisingly the between run overall reproducibility for the High *T pallidum* Antibody, Positive and Negative control was reported as 0.00% CV in Table I.B.2.1 (Page 221).
v) Trueness. A set of 6355 negative and 37 positive blood donor samples and a set of 200 negative clinical samples were tested by the device and a similar chemiluminescence assay. Overall agreement was 99.98% (95% confidence interval 99.91-100.00%) for blood donor samples and 100.00% (95% confidence interval 98.17-100.00%) for clinical samples.
vi) Cut-off. The optimal cut-off value was determined using a set of 7203 samples from blood donors and hospitalised individuals with diverse medical conditions. Receiver-operating characteristic (ROC) analysis determined that a 0.20 multiplier of the mean relative light units that measure the chemiluminescent reaction resulted in 99.9% specificity and 100% sensitivity.
vii) Specimen stability. Stability values were determined testing a minimum of 2 replicates of 10 negative plasma samples, 10 positive plasma samples, 10 negative serum samples, and 10 positive serum samples, although sample on-board storage experiments used only a single test result on each of two instruments (page 195). Positive samples used in the study were prepared as spiked samples rather than true patient samples. The device was reported to be stable for up to 14 days for samples stored at 2 to 8ºC, for up to 7 days for samples stored at approximately 30ºC, and for three or more months for samples stored at -20ºC or more. Stability was ensured up to six freeze/thaw cycles. On-board stability was assessed using positive and negative controls for up to 3 hours.

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

The analytical performance assessment conducted by the manufacturer was based on CLSI and FDA guidelines and standards. The analytical performance report assessed all relevant parameters required for qualitative detection of *Treponema pallidum* antibodies, except for the Limit of Detection (LoD). The justification of the manufacturer for omitting the specification of the LoD, based on the unavailability of NIBSC Code 05/132 WHO standard from the vendor and the fact that the device delivers qualitative results, is considered a shortcoming. LoD is an important parameter of performance that must be determined for both quantitative and qualitative assays, as stated by accredited standards (i.e. the Clinical Laboratory Standards Institute CLSI EP17 protocol). The extent of evaluation for the rest of analytical parameters was appropriate, including the use of a sufficient number of samples or replicates, the definition of suitable acceptance criteria, the conduct of adequate data analysis, and the reporting of acceptable values of performance. Procedures for evaluation of analytical performance were clearly defined.

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

The clinical performance report demonstrated sufficient ability of the device to yield results that were correlated with presence or absence of syphilis infection in blood donors and hospitalised individuals. Evidence for the evaluation of clinical sensitivity (diagnostic purpose) was gathered using 616 preselected positive samples: i) 400 having unknown disease state obtained from commercial providers and ii) 216 samples representing the full spectrum of syphilis infection from primary to tertiary syphilis. No additional information on how the clinical history was acquired, and no supplemental testing to verify the presence or absence of the disease was provided. A set of 6393 negative blood samples from random donors was used for evaluation of clinical specificity (screening purpose); and 200 hospitalised/diagnostic negative clinical samples were used for evaluation of clinical specificity (diagnostic purpose). One seroconversion panel for evaluation of seroconversion sensitivity was tested.

The set of 616 samples were tested by the device against at least two anti-*Treponema pallidum* tests. The reported global value of clinical sensitivity was 100.00% (95% confidence interval 99.40-100.00%) and specific values of clinical sensitivity were similarly high across all stages of syphilis infection. Clinical specificity was 99.95% (95% confidence interval 99.86-99.99%) and 100.00% (95% confidence interval 98.17-100.00%) for the intended uses of screening and aid to diagnosis, respectively. Acceptable positive and negative predictive values and likelihood ratios were also provided by the manufacturer.

All clinical performance parameters were assessed using a sufficient number of negative and positive clinical samples. Selected positive samples were representative of all the different stages of syphilis infection. Negative samples were randomly selected. The reference assays used for comparative clinical performance were adequate according to the state of the art. Acceptance criteria for values of clinical performance parameters were well defined. Values reported for clinical sensitivity and clinical specificity were optimal. However, a PMPF report was not available for assessment of device safety.

[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)

(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 approach taken by the manufacturer to gather clinical evidence addressed sufficiently the demonstration of scientific validity, analytical performance, and clinical performance. Scientific validity was based on the identification of evidence across reliable sources of information (accredited data bases of scientific publications, web sites of relevant public health institutions, appropriate literature search and selection). Analytical performance was acceptably evaluated following clearly defined procedures. Evidence of device clinical sensitivity was gathered using diverse collections of blood donor and clinical samples in sufficient number. The approach of the manufacturer to use a proportion of positive samples with unknown clinical status from commercial vendors was considered to be appropriate, given the low prevalence of syphilis infection in the target population.
2. The literature search methodology, protocol and report
The scientific validity report referenced an appropriate number of studies (n=29) that were retrieved from reliable sources of information to support the scientific validity of the device. A thorough literature search was implemented to identify some of these studies, as well as a detailed definition of the inclusion and exclusion criteria that were applied for selecting the most relevant ones.
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 on which the CMIA device is based is a well-known serological method that has been routinely used for screening and as an aid to diagnosis of syphilis in several developed countries over the last years. Similar on-market devices use the CMIA technology as well as other chemiluminescence-based methods for detection of *Treponema pallidum* antibodies.
4. Acceptability of clinical evidence (clinical data and performance evaluation results) against state of the art in medicine
Clinical evidence provided was concluded to be acceptable and was supported by sufficient results of scientific validity, analytical performance, and clinical performance. The majority of the references cited in the scientific validity report refer to studies published in recent years and are representative of the state of the art in medicine. Analytical performance of the device was assessed following CLSI and FDA guidelines and standards that are commonly used in clinical laboratories for validation of new devices. Device clinical performance was evaluated against state-of-the-art reference assays. Reported values of clinical sensitivity and clinical specificity are considered acceptable according to levels of diagnostic accuracy currently required in blood donor centres and clinical settings. Device safety could not be assessed due to unavailability of the PMPF report.

5. Adequacy of PMPF report(s), where applicable
A well-designed PMPF Plan was included by the manufacturer in the PER but no PMPF report was made available for review.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report
In general, the information of the PER provided sufficient clinical evidence of scientific validity, analytical performance, clinical performance. Data reported support the clinical benefit of using the device for the intended purposes. It is recommendable that the manufacturer be requested to provide further information regarding: i) The device LoD. ii) The PMPF report and data of device safety in operational conditions. iii) A final version of the manufacturer's instruction for Use/ package insert should be included in the PER.

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.

[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.

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

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

[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.