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	04/11/2021
Notified Body Number	2797
Internal PECP dossier #	IVD-2021-000009
***In vitro* diagnostic medical device**	This test is intended for the qualitative screening of blood and plasma donors for the detection of *Treponema pallidum* IgG and IgM antibodies to syphilis in human serum, EDTA plasma or CPDA 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)*	IgG and IgM antibodies to Treponema pallidum
P2	function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc*	Blood and plasma donor screening
P3	the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate *e.g. hepatitis C infection, exposure to SARS-CoV-2, risk of HIV transmission in blood transfusion etc.*	Syphilis
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*	Serum and plasma
P7	where applicable, the testing population *e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range*	Blood and plasma donors

P8	intended user	Professional Users - Blood donor centres
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.*	Haemagglutination assay

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group

Date of views	12/01/2022
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-9

3.2 Summary of expert panel views

The device is intended for the qualitative screening of blood and plasma donors for the detection of *Treponema pallidum* IgG and IgM antibodies to syphilis in human serum, EDTA plasma or CPDA plasma using a dedicated testing platform. The technology is based on the principle of agglutination of preserved avian erythrocytes, sensitized with extracted antigens of *T.pallidum* (Nichols strain) and relies on pattern recognition to determine reactivity. Positive and negative controls are provided with the device as separate components, with the intended use on a Class D device.

a) Scientific validity report

The scientific validity information was provided and detailed the clinical history of syphilis and testing approaches used in a clinical and blood screening setting. Information provided was accurate and relatively comprehensive. Summary of reference documents from several significant jurisdictions, including the European Union, were provided.

b) Analytical performance report

In general, the number of samples or replicates that were used to demonstrate analytical performance was sufficient, the data analyses performed were adequate, and reported values of analytical parameters were acceptable. However, certain aspects of analytical performance were insufficiently explained or were not available for assessment. The majority of samples used for assessment of precision had concentrations higher or much higher than the LoD (CLSI literature recommends using samples at LoD borderline concentrations).

The effect of possible interference was mainly evaluated by spiking in substances in normal samples and than re-evaluated on a significant smaller number of biological samples with natural presence of interferring substances. This is the case, for example, of hypertriglyceridemia where the of Intralipid that was supplied at 20% concentration: this situation cannot be superimposable to that of different levels of patients suffering from hypertriglyceridemia or anti-phospholipid antibodies. Use of further true biological samples with specific condition of high levels of lipids, haemoglobin, bilirubin etc. should be recommended in order to better evaluate the matrix effect. Interference studies state "Four reactive and four non-reactive samples were prepared". Although each evaluation was run in triplicate, this number may be deemed insufficient. These aspects are particularly important since it is reported that the positive rate of syphilis antibody of different genders increases with age. This factor, which can influence the rate of detection, could affect the analytical performance of the assay. This aspect was considered in the evaluation of the assay performance.

The panel of pathogens considered for evaluation of cross-reactivity did not include specific pathogens, such as human cytomegalovirus, that have been reported to have a noticeable prevalence rate among blood donors. Analyte concentrations in samples used for determination of the cut-off value were not reported.

Outcomes of studies describing the of Whole system failure rate; Clinical cut-off studies; Guardband studies and Carryover study were reported but scant protocols or evidence provided.

c) Clinical performance report

CLSI guidelines have been followed where applicable for the performance studies. Clinical sensitivity was evaluated by testing a panel of 826 commercially sourced, known TP positive samples. These samples originated from blood donors in the US and Europe. Additional sources of evidence included i) literature review, ii) external quality assessment scheme data, iii) testing of clinically staged syphilis samples and iv) seroconversion panels. Clinical specificity was determines using approximately 6660 unselected, delinked donors tested in three FDA accredited USA blood screening facilities. The comparator assay used for sensitivity and specificity was a non-CE IVD assay that uses similar technology to the IVD under assessment. Results generally agreed with reference results or comparator assay(s) test results.

The manufacturer provided a literature review with the stated intention to "association of an analyte with a clinical condition or a physiological state". The review did not present an analysis of the performance of the IVD in a blood screening setting or did it compare the results of the IVD with compariable assays with a similar intended use, considering that other similar methods have been recently published in this setting. The technology has been in use in Europe since 2019 and is commonly used in blood screening laboratories worldwide for the intended use. No evidence on device safety was provided.

In general, the information provided was appropriate, however the details on experimental protocol was lacking. Detailed protocols and results of testing were missing on many studies making evaluation of conclusions impossible. In some sections, a statement of acceptable performance was made by the manufacturer without any evidence. Given the low prevalence of syphilis among blood donors, the

approach chosen by the manufacturer to demonstrate clinical performance by combining sensitivity results on a set of commercially sourced positive samples with specificity results on a large set of negative samples collected in diverse blood donor centres (in addition to results on a small collection external quality assessment panel) was considered adequate.

No evidence to support the safety of the device was provided. The IFU provided states "A Summary of Safety and Performance shall be written for the user and, if relevant, to the patient. When Eudamed module is available link to current published SSP will be provided. Alternatively if another method is agreed link or description will be given."

No scientific validity report or literature review was provided as evidence of compliance with the IVDR. The clinical and analytical performance results were concluded to be acceptable. However, in some studies, insufficient evidence was provided for an assessment of the veracity of these conclusions and scant protocols were provided in some studies. It is recommendable that the manufacturer be requested to assess assay precision at LoD borderline concentrations (the majority of samples used for assessment had concentrations several times higher than the load LoD). Inclusion of cytomegalovirus in the cross-reactivity panel is advisable given the noticeable prevalence of this pathogen in the target population. The manufacturer should provide evidence on clinical performance using a larger set of clinical samples corresponding to early and late latent stages of syphilis, since lower bound limits reported for clinical sensitivity in these stages was rather low.

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 for review was accurate and relatively comprehensive and sufficiently demonstrated scientific validity. No literature review evaluating the device's technology against alternative technologies with similar intended use were provided. The regulatory environment for syphilis testing in blood products was well described and summarized main requirements and recommendations from WHO and relevant EU, USA, and UK public health institutions. No literature search methodology was specified for selection of scientific data.
2. Expert views on the analytical performance report[2]
The evidence provided supporting the analytical performance of the device was adequate. However, the level of detail of the protocols used, results obtained, and analysis performed was at times limited, making assessment of conclusions difficult. As an example, claims for reagent stability were made without evidence provided. In many studies, acceptance criteria of results were not provided. Where provided, the results of performance studies met the acceptance criteria.

[1] Annex XIII, Section 1.2.1 of Regulation (EU) 2017/746- Demonstration of the scientific validity
[2] Annex XIII, Section 1.2.2 of Regulation (EU) 2017/746- Demonstration of the analytical performance

The detailed assessment of analytical sensitivity was provided:

A range of analytical performance characteristics were assessed and reported. These include

i. **Limit of detection** – testing of three dilution series of WHO IS 05/132 was all less than 0.1 IU/mL. Precision - 5.2 Assay Precision section (page 20/43) reported lot to lot variation rather then assay precision. The 5.3 Reproducibility section (page 20/43) briefly described the experimental design but did not specify acceptance criteria. However, reproducibility was reported as 100% agreement with expected results.
ii. **Cross reactivity** - A total of 121 samples which were positive for potential cross reactants (infectious and autoimmune) were tested. No acceptance criteria presented. 2/121 repeat reactor reported, with one being confirmed as co-infected with syphilis.
iii. Analytical interference – A total of 132 T. pallidum positive samples, spiked with potentially interfering infectious and autoimmune substances, were tested. All 132 samples were detected by the device. In addition, T. pallidum positive and negative samples, spiked and unspiked with known concentrations of hemoglobin, bilirubin, triglyceride, intralipid and protein were tested on three reagent lots over an 8-day period to determine interference. All results were concordant with expected results and no difference in test results detected between days 0 and 8. There is no evidence of the reliability of these results on true hyperbilirubinemic, hypertriglyceridemic and hemolized biobanked plasma and sera (thawed and frozen several times).
iv. **Sample type equivalence** –25 samples drawn as serum and into K2 and K3 EDTA were spiked as negative, low and high positive for antibodies to syphilis. A further 40 samples matched serum and CPDA samples were all tested and qualitative results compared. Testing of all sample types on days 0 and 8 reported the expected result and equivalence between sample types was concluded.
v. **Sample storage** - 450 EDTA plasma samples and 450 serum samples were stored and tested for up to 7 days. Various numbers of samples tested on each day, ranging from 165 – 510 samples per day. No indication of sample reactivity was provided. Conclusion indicates storage temperature was 2-8°C. All results were concordant with comparator assay.
vi. **Microbial contamination** - Microbial interference studies were carried out following CLSI guidelines EP7-A2. Five positive and five negative samples spiked with *Candida sp*., *Escherichia coli*, *Pseudomonas sp*., *Staphylococcus sp*. and *Aspergillus sp*. Stored at 2-8°C for 16 days and tested on three reagent lots. All tests reported expected results demonstrating no inference by contamination.
vii. **Reagent stability** claims are reported (pages 30/43) but no supporting evidence is provided. Of note, 5.11 Additional sample handling studies claims sample storage at -20°C for one month, however no evidence is provided.
viii. **Controls reactivity** - Controls were pre-diluted at ½ and ¼ with diluent, each dilution tested five times. Each dilution gave expected results. No indication of storage conditions or length of storage was provided.
ix. **Air mix vs vibration mix equivalence** – 50 serum and 50 plasma syphilis negative samples and 603 known syphilis positive samples, as well as a dilution series of the WHO IS were tested in three reagent lots under both vibration and air mix modes. One of 603 positive samples was negative when tested using air mix mode. Substantial equivalence between modes was concluded
x. **Prozone effect**–Statement that device was not affected by prozone was made but evidence was not provided.

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

The clinical studies reported were adequate and appropriate. The results of testing indicated acceptable clinical performance. It is noted that the device is intended for screening blood donations

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

only and not for clinical or diagnostic testing. Only one seroconversion panel was tested due to lack of availability of commercial panels. Results of the device was comparable to an alternative device having similar intended use.

Clinical performance was assessed through: i) a study using a panel of commercially sourced positive samples (approximately 6660 specimens); ii) a study using positive samples collected at different stages of syphilis (35 specimens); iii) a study using external quality assessment scheme positive and negative samples (41 specimens); iv) a study using a seroconversion panel; and v) a multi-centre study in blood donor centres using unselected negative samples (approximately 6660 specimens). Clinical sensitivity reported in the study with commercially sourced samples was 99.76% (95% confidence interval 99.13-99.77%) for all serum, CPDA, and EDTA samples against clinical status. Clinical sensitivity reported in the study with staged syphilis samples was 100.00% (95% confidence interval 90.11 – 100.00%) against clinical diagnosis, although for early and late latent samples the lower bound limit of this optimal value was only 56.55%. The study with external quality assessment samples reported 100% concordance of results (95% confidence interval 91.4 – 100.0%). Clinical specificity reported against clinical status in the study with random blood donor specimens was 99.97% for plasma and 100.00% for serum.

The number of positive and negative clinical samples that were used to demonstrate clinical performance for screening was sufficient, the data analyses that were performed were adequate, device performance was compared to an alternative device as well as to clinical diagnosis, and values reported for these parameters were acceptable. To be noted, the manufacturer stated that no effort was made to exclude weak positive or samples containing potential interfering substances in the study with commercially sourced positive samples. In addition, negative samples were selected randomly in the multi-centre study in blood donor centres. These study design criteria were adequate to avoid potential selection biases.

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
Where information was provided for assessment, the approach taken by the manufacturer to gather clinical evidence addressed sufficiently the demonstration of scientific validity, analytical performance, and clinical performance. An appropriate literature review was conducted to determine the association of an analyte with a clinical condition or a physiological state (i.e. *T. pallidum* antibodies with syphilis). Meterological traceability studies were not conducted as the IVD is qualiative only. Evidence of analytical performance was reported for all parameters applicable for a qualitative assay. Evidence of clinical performance was gathered from diverse sources of information, including an extensive study using a panel of commercially sourced positive samples, a small study using positive

samples collected at different stages of infection, a study using external quality assessment scheme positive and negative samples, a study using a seroconversion panel, and a large multi-centre study using unselected negative samples. This multiple approach adopted by the manufacturer to demonstrate clinical performance was considered adequate, given the low prevalence of syphilis among blood donors and the difficulty to obtain positive samples prospectively.

2. The literature search methodology, protocol and report

A limited literature review was conducted and summarised, with 15 references submitted. Of these about four reviewed the clinical history of syphilis, and the others referenced aspects of blood screening. Given the intended use of the device, this was appropriate. However, a more detailed review of a more comprehensive set of references may have been advantageous, including performance evaluations of the device and comparisons with similar and alternative technologies. No literature search methodology was specified for selection of scientific data.

3. The technology on which the device is based, the intended purpose of the device and any claims made about the device's performance or safety

The technology used in the device under consideration is well accepted for the intended use and has been used widely for more than five years worldwide. The greatest adavantage of this device is its complete automation compared with other agglutination tests.

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

The evidence provided was adequate but not extensive. Detailed protocols were lacking in some instances, summary of study results was provided, but in some cases insufficient detail was provided to accurately assess conclusion.

An example is the conclusion of storage of samples at -20°C for one month and undergo 5 freeze-thaw cycles (page 30/43 - 5.11 Additional sample handling), where no evidence was provided. Throughout the document is reference to Clinical study Protocol Rev 1.0 and 4.0, as well as reports VR-001 to VR=0019 (with some exceptions), which seem to relate to additional documentation on supporting studies that was unavailable for review.

In general, values of clinical sensitivity and clinical specificity reported in the clinical performance studies were acceptable. However, the specific values of clinical sensitivity that were reported in the study with staged positive samples did not reach sufficient statistical validity for the early and late latent stages of syphilis (lower bounds of the 95% confidence interval were reported to be only 56.55%).

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

The manufacturer states in the PMPF report that no updates are required to the Performance Evaluation Report v01 (previous to the PER v02 under assessment). However, no information was provided about the extent of periodic safety or quality controls established to assess the adequacy of post-market performance follow-up performed by the manufacturer.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report
In general, the information provided for review covered relevant aspects of the IVDR legislation providing some evidence of device performance. The report does seem to refer to additional documentation including to Clinical study Protocol Rev 1.0 and 4.0 ad VR-0XX reports. A number of statements of compliance with particular requirements of the legislation were made without supporting evidence, while referring to these additional documents. Therefore, it is not possible for the reviewers to assess the veracity of these conclusions e.g. stability studies on page 30/43 clauses 5.9 to 5.13. Where data was provided, the level of evidence was adequate, without being comprehensive. Sufficient summary data was presented to allow for an assessment of the performance of the device, especially given the performance was mainly within appropriate acceptance criteria, and any deviations were explained. A more complete set of documents with greater detail of protocol, analysis and reporting would aid in the assessment of the conclusions made. It is recommendable that the manufacturer be requested to provide further information on the following aspects: i) Copies of documents referred to as evidence but not provided ii) Results of assay precision with a larger number of samples at LoD borderline concentrations iii) Results of cross-reactivity with human cytomegalovirus. iv) Results of a more extensive study with positive samples collected in the early and late latent stages of syphilis, since the values of clinical sensitivity that were reported in the study with staged positive samples for these disease stages did not reach sufficient statistical validity (lower bounds of the 95% confidence interval were reported to be only 56.55%). v) Where available, a literature review of independent or manufacturer-sponsored studies of the assay, including any comparator studies published over the past 5 years. vi) Evidence of safety of the IVD

3.6 Stakeholder information, where available

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

[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.

If yes, please summarise the information and how it was taken into account.
The document provided by the manufacturer refers to several supporting documents as evidence but which were not provided. These include the following documents: • PK7400 Clinical Study Report Rev 1.0 • PK7400 Clinical Study Report Rev 4.0 • Shelf life studies (VR-011 v01, VR-011 v02, VR-011 v04) • Opened vial stability (VR-012 v01) • On board stability and Reagent in-use in PK Reagent vial (VR-013 v01) • Additional sample handling studies (VR-007 v01 and VR-007 v02, VR-006 v01) • Shipping Studies (VR-008 v03) No evidence of IVD safety was provided for assessment. The assessment of adequacy of evidence was undertaken where it was provided. Otherwise, it was noted in the assessment where evidence was lacking.

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
No divergent positions occurred

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

[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.