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	22/09/2021
Notified Body number	2797
Internal PECP dossier #	IVD-2021-000002
***In vitro* diagnostic medical device**	This test is intended to screen donor samples for HEV RNA in plasma samples from individual human donors, including donors of whole blood, blood components (red cells, platelets, and plasma), and other living donors.

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)*	Hepatitis E virus (HEV)
P2	function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc*	This test is intended for use to screen donor samples for HEV RNA in plasma samples from individual human donors, including donors of whole blood, blood components (red cells, platelets, and plasma), and other living donors.
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.*	Hepatitis E virus (HEV) transmission in blood transfusion
P4	whether it is automated or not	Automated
P5	whether it is qualitative, semi-quantitative or quantitative	Qualitative
P6	type of specimen(s) *e.g. whole blood, serum, saliva etc*	Plasma
P7	where applicable, the testing population *e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range*	Living donors of whole blood and blood components.
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,*	Real-time PCR

	sandwich immunoassay, competitive immunoassay, immunoturbidimetric assay etc.	

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group

Date of views	08/11/2021
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-2

3.2 Summary of expert panel views

The nucleic acid amplification test (NAT) assay under evaluation is an on-market product under Directive 98/79/EC (*In-vitro* Diagnostics Directive; IVDD), as of August 2014. The assay under evaluation is a qualitative nucleic acid amplification test for the direct detection of hepatitis E virus (HEV) RNA (genotypes 1-4) in human plasma. The intended use of the assay is to screen human donor samples for HEV RNA, including donors of whole blood, blood components (red cells, platelets, and plasma), and other living donors. Plasma from all donors may be screened as individual samples. For donations of whole blood and blood components, plasma samples may be tested either individually or plasma may be tested in pools comprised of aliquots of individual samples. This test is not intended for use on samples of cord blood or for use as an aid in diagnosis for HEV.

The scientific validity report, the analytical performance report and the clinical performance report show, with an acceptable residual risk, that the NAT assay under evaluation fits its intended use and appears to be fit for purpose.

We consider the manufacturer's justification acceptable for the approach to gather the clinical evidence. Literature search was conducted using a sufficiently robust methodology, and the summary of literature adequate, supporting the manufacturer’s in-house evidence, protocols and reports’ conclusions.

The NAT is recognized as appropriate technology for screening for transmissible agents in blood banks. The systematic introduction of this technology since the 1990s substantially reduced the seroconversion/window period for several pathogens, including HEV. Thus, the manufacturer's selection of this technology guarantees a lower risk of post-transfusion of HEV infection.

Safety warnings and precautions are deemed to be adequate for the materials that make up the kit. The reported performance evidence is suitable for the intended use of the IVD. Clinical evidence consisted of scientific validity, analytical performance and clinical performance. The measurements and analyses were sufficiently acceptable in demonstrating the ability of the HEV NAT to correctly classify the results based on the samples tested.

Acceptance criteria was defined by the manufacturer, as follows: the clinical specificity of the assay must be equal to or greater than 99.9% for plasma specimens from living donors, assuming a zero-prevalence population. The clinical sensitivity must be 100% reactive in the initial testing. These values meet the targets admitted in most European blood banks. All genotypes must be reactive at 3-5 times the limit of

detection. Endogenous and exogenous interfering substances must be negative, and spiked sample with interfering substances must be reactive. Evidence provided by the manufacturer met the specified acceptance criteria.

To conclude, the manufacturer presents protocols and reported evidence that follow the terminology and requirements contained in REGULATION (EU) 2017/746. The Performance Evaluation Report presents, with robust support, a NAT suitable for its intended use in the blood bank.

Note: The pages referred to follow the pagination of the PDF that compiles the manufacturer's Performance Evaluation Report and Referenced Documents.

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 of the assay performance evidence is documented in the scientific validity report (page 338-358). The manufacturer has demonstrated the scientific validity of the device measuring the HEV RNA (genotypes 1-4), supplemented with a comprehensive literature review of the peer-reviewed scientific literature using keywords relevant for this project. Consensus expert opinions/positions from relevant professional associations are published in peer-reviewed journals such as “Transfusion” (impact factor (IF) 2020 of 3.157). These articles include a clinical and analytical performance of the device. Two publications reported less favourable findings, publications with controversial findings were included.
2. Expert views on the analytical performance report[2]
The manufacturer demonstrates the analytical performance of the device (page 297-302) in relation to all the parameters described in Table 1 (page 300). Overall, the evidence provided supports the analytical performance claims of the manufacturer, indicating the IVD is fit for purpose. The 95% hit rate detection limit (determined using the Probit regression model) was 18.6 IU/mL depending on the estimate in three different batches. In these lots, the 95% was between 12.6 and 27.9 IU/mL (page 175-177). Reactivity was tested in 23 HEV samples for Genotypes 1 (three samples), 2 (one sample), 3 (10 samples), and 4 (9 samples). All samples were reactive (page 183-184). Metrological traceability to reference preparations of higher order is given by using the respective WHO International Standard and its unitage (IU). In regard to parameters that were omitted, the limit of quantification, measuring range, and linearity studies were not performed, the manufacturer arguing that the test is qualitative 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 quantification, measuring range, and linearity were not conducted." The manufacturer concluded that, based on the results of the studies, the test “shows acceptable performance, demonstrating that” the device “is suitable for its intended purpose and detects analysis with sufficient accuracy and precision” (page 302).

[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 study of the clinical sensitivity/clinical sensitivity trade-off suggested a set of cut-offs between relative fluorescence intensity (RFI) from 1.05 to 2.1, for which both proportions are 100%. From a theoretical point of view, the manufacturer seems to favor clinical specificity over clinical sensitivity; that is, it favors the risk of false negatives over false positives. However, RFIs between 1.05 and 2.1 show the same diagnostic performance as shown in the ROC curve with an illustrated area under the curve of one (100% true results) (Figure 1, page 191).
3. Expert views on the clinical performance report[3]
The clinical specificity is 100.0 %, with a two-sided 95% confidence interval of 99.6% - 100%. The value hits the target of 99.9%. The study used "1000 negative EDTA plasma specimens". These specimens were obtained from healthy donors, which can be interpreted as a negative clinical diagnosis for HEV infection. The clinical sensitivity is 100.0 %, with a two-sided 95% confidence interval of 99.3% - 100%. The value hits the target of 100% (page 211). All samples were 100% reactive when tested neat and/or at 5x Limit of Detection (LOD), demonstrating that the device can detect genotypes 1 - 4. Sensitivity evaluated was by testing 100 clinical EDTA plasma specimens that were NAT-positive for HEV. Part of these samples (33) was diluted with negative EDTA plasma. The manufacturer appears to consider "NAT-positive for HEV" as a "gold test" for HEV infection. Otherwise, it would be designated clinical "sensitivity" as "positive agreement".

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 manufacturer has compiled comprehensive evidence on the clinical performance of the assay to support its intended use, as detailed in the Clinical Validation Plan DH-302-008 (page 305) and reported in the Clinical Performance Report and Clinical Validation Report DH-302-008B (page 318). The manufacturer states “No clinical performance studies have been executed for the assay under IVDR that would require referencing under Annex XIII Section 1.2.1. D, Demonstration of compliance to Annex XIII Section 2 is not applicable because the studies that generated substantial and relevant data predate IVDR enactment and therefore have been provided as other sources of clinical performance data.” (page 333). However other sources of clinical data are provided including evidence on genotype detection, specificity, correlation with another HEV NAT assay, and sample stability. The evidence provided is adequate to demonstrate the intended clinical benefits.
2. The literature search methodology, protocol and report
The requirement as outlined in IVDR Annex XIII Section 1.3.2 Indent 2 was met using a comprehensive

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

literature search as detailed in "Scientific Peer-review Literature" (page 393) and Table 3: Literature Searches in Support of Scientific Validity. A total of 15 peer-reviewed papers addressing the use of NAT for donor screening and 10 on the use of NAT for HEV screening were identified. A summary of additional publications addressing Analytical and/or Clinical Performance of Hepatitis E Virus Nucleic Acid Tests were provided, including publications that were less favourable to the manufacturer's assay. All aspects of the review of the performance of the assay were addressed adequately.

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 is based on nucleic acid test technology which includes nucleic acid extraction and purification followed by PCR amplification and detection by probes labeled with fluorescent dyes. Nucleic acid test technology has been used in blood donor screening to decrease the "window period" between initial infection and the antibody detection for over a decade and is considered "state of the art". The use of this technology is fit for purpose. The assay under consideration has no significant innovations and has been in use in the market in Europe since August 2014. The literature search provided by the manufacture reviewing real-life usage indicates no performance or safety concerns.

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

The clinical evidence provided in the dossier is incorporated in two documents a) System Clinical Validation Plan (DH-302-008; page 303) and b) Scientific Validity Report (DH-302-322; page 378). The System Clinical Validation Plan includes approaches to assess a range of performance characteristics including LOD, genotype detection, specificity, correlation, cross reactivity, endogenous and exogenous interference, reproducibility and stability of samples and reagents. The Scientific Validity Report presented a comparison of the performance of the assay under investigation with a peer assay, as well as the results and summary of the literature search. The clinical evidence provided by the manufacturer was sufficient to determine suitability of the assay to safely be utilised for its intended use in blood donors screening populations.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report

The evidence provided by the manufacturer was comprehensive, and systematically structured with ease of reference of each document against the relevant clause in Regulation (EU) 2017/746 (IVD Regulation; IVDR). Table 1. "Required Content of the Performance Evaluation Report and Compliance Status" (page 11) documents each of the relevant clauses of the IVDR, a summary of the content of each relevant document and the title and document identification of the related manufacturer's evidence. In providing the evidence in this manner, each of the requirements of the IVDR could be easily identified and the relevant evidence reviewed. On review of the evidence, all relevant aspects of the IVDR requirements were addressed in a satisfactory manner. The assay under review demonstrated appropriate levels of both clinical and analytical sensitivity and specificity. Sufficient evidence was presented on the robustness of the assay. The sample types included in the instructions for use, along with their storage conditions were validated. Detection of all four known genotypes of HEV was demonstrated. The technology used by the manufacturer is estimated as representing "state of the art" and is commonly

used in blood donor screening. No significant innovations are employed by the manufacturer. The assay has been in common use in Europe as a donor screening assay since August 2014 and many peer-reviewed papers have been published on its performance in a screening setting and in comparison, with other like assays. It is the opinion of the reviewers that the evidence provided by the manufacturer demonstrates the assay is fit for purpose and complies with the requirements of Regulation (EU) 2017/746.

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.
TEXT

3.7 Divergent positions in case no consensus can be reached

In case no consensus on the views can be achieved[5], please summarise divergent positions
There were no divergent opinions of the reviewers

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

[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.