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	21/09/2021
Notified Body number	2797
Internal PECP dossier #	IVD-2021-000001
***In vitro* diagnostic medical device**	This test is intended to quantify parvovirus B19 DNA alone or to simultaneously quantify parvovirus B19 DNA and detect HAV RNA in plasma intended for further manufacture collected from donors of whole blood, blood components, or 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)*	– parvovirus B19 genotypes 1, 2, and 3 DNA – Hepatitis A virus (HAV) genotypes I, II, and III 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 use as an in-process test to quantify parvovirus B19 DNA alone or to simultaneously quantify parvovirus B19 DNA and detect HAV RNA in plasma intended for further manufacture collected from donors of whole blood, blood components, or plasma.
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.*	Parvovirus B19 and HAV transmission in blood transfusion
P4	whether it is automated or not	Automated
P5	whether it is qualitative, semi-quantitative or quantitative	Parvovirus B19 is quantitative; HAV is 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*	Donors of whole blood and blood components. Organ and tissue donors.
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

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group

Date of views	22/11/2021
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-1

3.2 Summary of expert panel views

The proposed assay is an *in vitro* Nucleic Acid Test (NAT) for the detection of both Hepatitis A virus as well as Parvovirus B19, based on real-time amplification polymerase chain reaction technology. This test is intended for use as an in-process test to quantify parvovirus B19 DNA alone or to simultaneously quantify parvovirus B19 DNA and detect qualitatively HAV RNA in plasma intended for further manufacture collected from donors of whole blood, blood components, or plasma. Genotypes 1, 2 and 3 are detected for B19, and the genotypes I, II and III are detected for HAV. The detection of B19 is quantitative using the WHO International Standard for B19 DNA as reference material for calibration of the assay, while the detection of HAV is qualitative, also using the WHO International Standard for HAV-RNA as reference for the limit of detection (LoD). Both assays are fully automated and can be performed on individual as well as pooled samples of plasma material from donors. The test is intended for screening blood or blood components specifically and not for routine clinical diagnostics. This test is not intended for use on samples of cord blood or for the diagnosis for parvovirus B19 or HAV infections.

The assay is already on the European market under the *In Vitro* Diagnostic Directive, since 12 March 2015. The supported Performance Evaluation Report (PER) documents, describe the characteristics and performance of the assay according to the requirements mentioned in the Performance Evaluation Report (Table 1, page 12-15) and is in compliance with the IVDR guidelines.

The approach by the manufacturer is in line with current state-of-the-art technologies. The approach chosen by the manufacturer is straightforward and indicates no safety issues with the technology and the device used.

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]
Clinical performance data have been described in document DH-275-349 (page 634-678). No specific clinical studies have been performed under IVDR. There were three (3) clinical studies and six (6) analytical studies performed with clinically derived positive HAV or B19 positive materials, showing that the system had a robust medical value for the quantitative detection of B19 and a qualitative detection of HAV according to the required specifications defined in the European Pharmacopoiea. A comparison with competitor assays was performed, and an extensive literature review demonstrated a consistent performance across several sites for the intended use, in which independent groups of experts and government organisations were involved. A list of peer reviewed publications of the data, abstracts, and guidelines (both from U.S.A. and European), are available. Also, the scientific validity supports the need for screening blood for HAV and parvovirus B19 due to the risk of transfusion transmission as well as the NAT methods are the most appropriate for blood screening compared with other current diagnostic methods.
2. Expert views on the analytical performance report[2]
The analytical performance of the device is described in document DH-275-480 (page 407-412) and the manufacturer demonstrates that the test shows acceptable performance and it is suitable for its intended purpose with sufficient accuracy and precision. The manufacturer has evaluated all the parameters described in Table 1 (page 410) and has compiled comprehensive evidence on the analytical performance of the assay in relation to different parameters, such as specimen type and its stability, trueness, precision (repeatability for HAV and linearity for Parvovirus B19), analytical sensitivity (limit of detection), analytical specificity (cross-reactivity), and cut-off. The LoD of the test for HAV RNA and parvovirus B19 DNA were determined using the WHO International Standards for HAV RNA (NIBSC code 00/560) and parvovirus B19 DNA (NIBSC 99/802). The LoD for HAV RNA was determined as 1.1 IU/ml (95% CI 0.9-1.3) and for B19 DNA the LoD was

[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

determined as 13.9 IU/ml (95% CI 11.7-17.4), both measured in plasma. The LoD data are the results of testing different lots of the assays involved.

In 2004, the European Pharmacopoiea required that B19 DNA levels must be below 10.000 IU/mL in manufacturing pools used for production of human anti-D immunoglobulin and pooled human plasma treated for virus inactivation. European regulatory requirements mention that if HAV NAT tests are used on the manufacturing pool as part of in-process testing, the test be capable of detecting a control containing 100 IU/mL HAV RNA. Both assays do fulfil these requirements.

Also, in regard to analytical sensitivity the assay ensures consistent detection of HAV genotypes I, II and III, and all relevant Parvovirus B19 genotypes (1, 2 and 3a).
Finally, the assay shows that the diagnostic sensitivity and specificity (for HAV and B19), quantitation (for B19) are not affected in the presence of known relevant endogenous and exogenous interfering substances and cross-reactive materials.

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

Demonstration of clinical performance is documented in the Clinical Performance Report and Clinical Validation Report (DH-275-008B). The clinical performance of the test has been based on a combination of analytical performance data, other sources of clinical performance data, and scientific peer-reviewed literature.

The LoD of the assay for HAV RNA and parvovirus B19 DNA were determined using the WHO International Standards for HAV (NIBSC code 00/560) and parvovirus B19 (NIBSC 99/802). The LoD for HAV was measured as 1.1 IU/ml (95% CI 0.9-1.3) and for B19 the LoD was measured as 13.9 IU/ml (95% CI 11.7-17.4), both measured in plasma. In 2004, the European Pharmacopoiea required that B19 DNA levels must be below 10.000 IU/mL in manufacturing pools used for production of human anti-D immunoglobulin and pooled human plasma treated for virus inactivation. European regulatory requirements mention that if HAV NAT tests are used on the manufacturing pool as part of in process testing, the test be capable of detecting a control containing 100 IU/mL HAV RNA. Both assays do fulfil these requirements.

Diagnostic specificity and diagnostic sensitivity are the main statistical measures of clinical performance in blood donor screening tests.
Diagnostic specificity was determined for both Hepatitis A virus (HAV) and Parvovirus B19. The specificity of the assay must be [redacted] plasma specimens from living donors. The specificity for the assay is 99.9% for Parvovirus B19 and 100% for HAV in EDTA-plasma. The two-sided 95 % confidence interval limits are 99.4% - 100% for Parvovirus B19 and 99.6% - 100% for HAV. The assay demonstrated a false positive rate of 0% which was less than the target requirement of 0.5%. The calculated cross contamination rate is 0% with a two-sided 95% Confidence Interval of 0% - 1.53 %.

Sensitivity (computed as “positive agreement”) of HAV in different matrices for nine anticoagulant matrices was from 96 to 100% (page 512).

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

Agreement between deconstruction results (all 6 layouts for pools of 96) and the known sample types: result of “Reactive” was obtained when a sample tested HAV reactive and/or B19 ≥ cut-off in a resolution pool (*n* = 32). A final result of “non-Reactive” (*n* = 544) was obtained when a sample tested HAV-Non-reactive and B19 < cut-off in a pool of any size. Positive agreement (referred to as “overall sensitivity”), negative agreement (referred to as “overall specificity” and overall agreement were all 100% (page 529).
Agreement between deconstruction results (all 5 layouts for pools of 480) and the known sample types (page 547): final result of “Reactive” was obtained when a sample tested HAV-reactive and/or B19 ≥ cut-off in a resolution pool (*n* = 27). A final result of “non-Reactive” was obtained when a sample tested HAV-Non-reactive and B19 < cut-off in a pool of any size (*n* = 2,373). Overall Percent Agreement, Overall Sensitivity and Overall Specificity were all 100%. The device accurately identifies HAV and parvovirus B19 reactive samples, both in pools of 96 samples and pools of 480 samples (0% false negatives).

Despite it is referred “The overall sensitivity was 100% (32/32; 1-sided score 95% lower bound confidence limit 92.2%) for pools of 96 and 100% (27/27; 1-sided score 95% lower bound confidence limit 90.9%) for pools of 480” (see page 472), the manufacturer has not evaluated the diagnostic sensitivity, such as referred to in CLSI EP12-A2, since it was not used for diagnosed individuals samples, but positive samples in comparative tests, similar to some published studies (see page 649). Although it can be seen as a limitation of the study, it is likely to happen with agents with a low prevalence, where, typically, it is replaced by the calculation of the positive agreement. The limitations of this approach are related to the clinical performance of the comparative test (which is not a "gold standard").

Reproducibility was established for HAV and parvovirus B19 across all 5 protocol parameters (lot, site, day, batch, and with-in-batch).

In regard to parameters that were omitted, such as positive predictive value, negative predictive value, and likelihood ratio, expected values in normal affected populations, are not utilized in blood donor screening tests.

Mathematical equations are not always consistent with the CLSI EP12-A2 technical guide. Diagnostic sensitivity and specific are computed as “positive agreement” and “negative agreements” due to be used “total valid results” instead “number of positives according to diagnostic accuracy criteria” and “number of negatives according to diagnostic accuracy criteria”, respectively (see page 510). Also, the terminology is not always consistent with EP12A, as when positive agreement is referred to as “overall sensitivity”.

In conclusion, the assay is suitable for the intended purpose and the performance is acceptable according to the European guidelines.

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 provided a clinical performance report and a clinical validation report (DH-275-008B, page 448-473). The manufacturer has performed no additional clinical performance studies but has provided additional analytical studies with clinical samples and clinical studies (see Table 3 and 4 respectively) to provide evidence as other sources of clinical performance data. These data also include retrospective analysis of data generated prior to the enactment of the IVDR. Additional information on diagnostic sensitivity and specificity, genotype detection, correlation with another assay, linearity (for parvovirus B19) and precision, clinical specimen stability, reproducibility (across lot, site, day, and batch), and detection from pooled samples, is provided. The evidence provided is adequate to demonstrate the intended use of the method.
2. The literature search methodology, protocol and report
The requirements as outlined in IVDR Annex VIII section 1.3.2 were met using a comprehensive literature search as outlined in DH-275-008B "Scientific peer-reviewed literature" (page 473-479) and Table 5 (page 475) in which the summary of the literature search is described based on the search terms or the string queried. In the Scientific Validity Report (DH-275-349) the manufacturer has developed a suitable literature search methodology and has compiled a lot of publications that support the scientific validity of the assay. A significant number of publications could be found for both using the system for the detection of HAV and parvovirus B19, and an additional three (3) conference abstract were found describing the analytical and/or clinical performance of the system for screening blood or plasma pools. The literature search report shows a summary of relevant publications in peer-reviewed journals such as *Journal of Clinical Microbiology* with impact factor (IF) 2020 of 5,948. The literature report shows 9 publications that support the scientific validity for the use of NATs generally, and 21 publications that support the HAV and parvovirus B19 NATs specifically for donor screening. Also, the report shows 3 publications describing the analytical or clinical performance of the assay, 12 publications describing the analytical or clinical performance of the device predecessor, 2 publications describing the performance of the primary competitor, and 4 other publications about tests that can detect HAV or parvovirus B19 that are used for donor screening. No publications were found with a less favourable or controverting findings, and no other published experience gained from routine diagnostic testing was found at the time that the literature search was done.

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 device is based as well as the intended purpose of the device are detailed in document ART7175469001 (page 17-53).
The test is based on real time PCR technology: nucleic acid extraction and purification followed by PCR amplification and detection. Viral nucleic acids from the donor samples are released by proteinase and lysis reagent, and impurities are removed. Primers selected from highly conserved regions of the viral nucleic acid provide a selective amplification of target virus from the donor sample. Specific B19, HAV, IC, and QS detection probes are each labeled with one of four unique fluorescent dyes, which are measured at defined wavelengths, thus permitting simultaneous detection and discrimination of the amplified B19, HAV targets, IC, and QS.

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 March 2015.
The intended purpose of the device is to quantify parvovirus B19 DNA and detect HAV RNA in plasma for further manufacture collected from donors of whole blood, blood components, or plasma.

The Risk Management Report (DH-275-027) contains the summary of the device risk and safety and the justification that the overall benefits outweigh the risks. There has been a risk-assessment performed and each of the individual risk's levels have been justified as acceptable and within the comparable state of the art technologies. The benefits of the product justify the overall residual risk acceptability (page 153-154). There have been no performance or safety concerns reported.

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

The clinical evidence is provided in two documents: Clinical Performance Report and Clinical Validation Report (DH-275-008B, page 447-487) and Scientific Validity Report (DH-275-349, page 634-678).
In the document DH-275-008B, both the clinical performance report and the clinical validation report is included. The clinical performance data included several analytical studies. Also included were clinical specimens' stability studies. Acceptance criteria for specificity and for exogenous substances were established and met. Only for high concentrations of hDNA at 4 mg/l, interference was identified but the acceptance criteria were [redacted] the assay could reasonably expect to meet or exceed the acceptance criteria. Cross contamination and variability of the assay was established. These results indicate that the assay is reproducible over multiple days, operators, reagent lots, instruments, and replicates per run. Acceptance criteria for several blood collection methods (anticoagulant) were established. As well as storage and transport conditions.

Demonstration of the clinical performance of the device has been based on a combination of analytical performance data, including genotype inclusivity, correlation studies, linearity, and precision studies. These data furthermore demonstrate performance, safety, and efficacy of the assay and establish robust medical value for the detection of HAV and parvovirus B19 in the intended use population.

In conclusion, this report describes the evidence generated from a retrospective evaluation of analytical studies, other sources of clinical performance data, and findings from scientific peer-reviewed literature that establish the overall clinical performance of the assay. Finally, the document DH-275-349 describes the state-of-the-art determination for the detection of HAV RNA and parvovirus B19 DNA in donor samples and establishes that the device qualifies as state of the art in medicine. In summary, the clinical evidence provided by the manufacturer was sufficient to determine suitability of the assay to safely be utilised for the intended use.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report
The information provided by the manufacturer is a very comprehensive and complete overview. Clear relation is provided in Table 1 between IVDR regulation (page 12-16) and the documentation provided in the "Performance Report and Compliance Status". The data provided gives an overview on the analytical sensitivity and specificity and the clinical value of the assay for the intended purpose according to European Guidelines. The assay is already in use since 2015 and undergoes continuous post-market monitoring, including complaint and complaint trend evaluation, and customer feedback as well as from scientific publications and abstracts. No deviations were reported. The technology is state-of-the art. The information provided by the manufacturer shows its compliance with the IVDR requirements. There are no additional recommendations for the manufacturer.

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

[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
No divergent opinions by the experts

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.