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	20/12/2021
Notified Body number	0123
Internal PECP dossier #	IVD-2021-000014
***In vitro* diagnostic medical device**	Chemiluminescent microparticle immunoassay (CMIA) for the qualitative detection of IgG antibodies to Epstein-Barr Virus (EBV) Viral Capsid Antigen (VCA) in human serum and 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)	
what is detected and/or measured *please specify the analyte(s) or marker(s), e.g. SARS-CoV-2 spike protein, Kel1 (K)*	IgG antibodies to Epstein-Barr Virus (EBV) Viral Capsid Antigen (VCA)
function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc.*	• aid in the diagnosis of infectious mononucleosis (IM) • aid in determining the stage of EBV infection
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.*	infectious mononucleosis
whether it is automated or not	Automated
whether it is qualitative, semi-quantitative or quantitative	Qualitative
type of specimen(s) *e.g. whole blood, serum, saliva etc.*	• Human Serum and Plasma
where applicable, the testing population	• Individuals suspected to have acute mononucleosis • Potential organ donors / organ recipients

e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range	
intended user	For Laboratory Professional Use Only
Technology (T)	
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	16/02/2022
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-14

3.2 Summary of expert panel views

Device description:

Epstein-Barr virus (EBV), also called human herpes virus 4 (HHV-4), is one of the most common viruses in humans. EBV is a lymphotropic, enveloped double-stranded DNA virus. It belongs to the herpesviridae family, subfamily gamma herpes viruses. In adults > 25 years the seroprevalence is > 95%. The virus is mainly transmitted by saliva, but sexual or transmission via transplantation or donated blood products is also possible. EBV is the causative agent of infectious mononucleosis and is also associated with Burkitt's lymphoma and nasopharyngeal carcinoma.

Specific antibodies (IgG and IgM) against EBV viral capsid antigen (VCA) are produced on exposure to EBV infection. IgM and IgG antibodies directed against VCA have high sensitivity and specificity for diagnosing EBV infection and infectious mononucleosis. Serologic tests are used for staging of the infection, to differentiate EBV infection from other infections with similar clinical symptoms and to determine the immune status in transplantation donors and recipients. For infection stage determination, tests for detection of IgM and IgG antibodies to EBV VCA and IgG antibodies to Epstein-Barr Nuclear Antigen-1 (EBNA-1) are commonly used.

This device described in this PER is intended for qualitative detection of IgG antibodies to EBV viral capsid antigen (VCA). In conjunction with other assays (EBV VCA IgM, EBV EBNA-1 IgG) this device is an aid in the diagnosis of infectious mononucleosis including the stage of the EBV infection. A second purpose of the device is the determination of EBV immune status in organ donors and recipients prior to transplantation. The device is to be used with an automated serology robotic system supplied by the manufacturer. The technology is an automated two-step immunoassay using chemiluminescent microparticles (CMIA). The chemiluminescent reaction is measured as relative light units (RLU). The presence or absence of EBV VCA IgG is determined by comparing the signal in the reaction to the cut-off signal determined from an active calibration curve.

Views on the performance evaluation report:

a) The scientific validity report.

The scientific validity report supports the use of Epstein-Barr Virus (EBV) Viral Capsid Antigen (VCA) Immunoglobulin G assay as an aid in the diagnosis of infectious mononucleosis, in determining the stage of EBV infection and in determining EBV immune status in organ transplant donors and recipients prior to transplantation as per the requirements of the *In Vitro* Diagnostic Device Regulation (EU) 2017/746 (IVDR).

The scientific validity report provides adequate background on EBV. Evidence contained in the report was sufficient to support the suitability of using a CMIA-based device based for detection of EBV VCA to diagnose infectious mononucleosis, determine the status of EBV infection, and determine the EBV immune status of organ donors and recipients.

b) The analytical performance report.

The manufacturer has determined the analytical performance parameters based on the intended purpose of the device. The manufacturer demonstrates that the test shows acceptable performance and it is suitable for its intended purpose with sufficient accuracy and precision.

The analytical performance report assessed all relevant parameters required for qualitative detection of EBV VCA antibodies, except for the parameter of analytical sensitivity. The statement of the manufacturer that no external recognized reference material is available for determination of analytical sensitivity is considered a shortcoming. The extent of evaluation for the rest of analytical parameters was appropriate, including the use of a sufficient number of samples or replicates. No sample used in the clinical performance studies was collected from organ donor centres to prove suitability of the device for determining the EBV immune status of organ donors and recipients.

c) The clinical performance report.

Clinical performance parameters were determined based on the intended purpose of the device. Overall analyses sensitivity and specificity are high and acceptable for the intended purpose of the test as diagnostic and screening assay.

The clinical performance of the assay has been demonstrated through internal and external evaluations using clinical specimens from patients tested for Epstein-Barr virus in human serum and plasma, and by comparison to existing on market approved assays for the same analyte and intended uses. A review

of available data for the EBV VCA IgG assay and other similar products was performed to determine if the product is state of the art in regard to analytical performance and ability to meet its intended purpose, providing medically relevant information necessary for successful patient management. 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 and values reported for these parameters were acceptable.

Views on the specific aspects of the performance evaluation report:

The manufacturer has provided clinical evidence based on scientific validity, analytical performance, and clinical performance data. Literature search strategy and the literature protocol are acceptable.

The appropriateness of the technology to reach the intended purpose of the device and the manufacturer's claims about the performance and safety of the device is in agreement with IVDR. The use of this technology assay is fit for purpose.

Views on the adequacy of the approach chosen by the manufacturer to evaluate and ensure performance and safety of the device:

The overall risk associated with the assay is comparable to 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 performance and safety of the device.

Overall conclusions and recommendations on the performance evaluation report:

In summary, overall, the experts were positive about the content and extent of the submitted dossier. The information of the PER provided sufficient clinical evidence of scientific validity. Analytical performance evaluation excludes assessment of analytical sensitivity, which is considered a shortcoming. Organ donor samples were not included in clinical performance evaluations. Therefore, the suitability of the device for intended purpose of determining the EBV immune status of organ donors and recipients has not been proved. Several recommendations for improvement of the assay evaluation are summarized in section 3.5.

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 supports the use of Epstein-Barr Virus (EBV) Viral Capsid Antigen (VCA) Immunoglobulin G assay as an aid in the diagnosis of infectious mononucleosis, in determining the

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

stage of EBV infection and in determining EBV immune status in organ transplant donors and recipients prior to transplantation as per the requirements of the *In Vitro* Diagnostic Device Regulation (EU) 2017/746 (IVDR).

The manufacturer's scientific validity report is organized per claim. i) Aid in diagnosis, ii) aid in determining stage of infection, iii) aid in determining immune status for transplantation. For all claims a literature search was performed including literature up to 2021.

The manufacturer has carried out a review of existing literature and available study data to collect sufficient clinical evidence to establish the use of the Epstein-Barr Virus (EBV) Viral Capsid Antigen (VCA) IgG antibodies for the intended purpose stated above. The search is extensive and provides sufficient recent evidence for the scientific validity. There are included articles from different geographical locations. The literature review of the peer-reviewed scientific literature uses keywords relevant for the subject and comparison to one other device measuring the same marker.

Data support the safety, effectiveness, and scientific validity of the assay. Collectively, the evidence supports that the assay is consistent with the generally acknowledged state of the art for its intended purpose. Additionally, the medical value and public health benefit outweigh the potential risks of the product.

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

Analytical performance parameters have been determined based on the intended purpose of the device. In absence of published common specifications the manufacturer has used the draft common specification for the analytical performance evaluation. It is expected that the final common specifications will not differ significantly from the draft. Assessment against the final common specifications will be performed and tracked via the post market surveillance process.

All analytical performance characteristics from the draft common specifications have been addressed by the manufacturer. In regard to parameters that were omitted, such as the limit of detection, limit of quantitation, accuracy, measuring range and linearity studies were not performed, the manufacturer arguing that they are not applicable as the assay is qualitative with result interpretations of non-reactive or reactive.

The analytical report assessed the following analytical parameters:

i. The manufacturer has evaluated the suitability of the most common sample collection tubes type for serum and plasma, obtaining that 8 different blood collection tubes were acceptable for this assay.
ii. The studies conducted to evaluate the effect of specimen handling under various storage conditions and time periods when testing serum and plasma specimens show acceptable results, and samples can be stored for up to 14 days at a storage temperature of 2 to 8°C on the cells/clot, up to 3 days at room temperature on the cells/clot and up to 3 freeze/thaw cycles after 14 days storage at 2 to 8°C on the cells/clot.

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

iii. The manufacturer has studied sample on board stability and met the acceptance criteria when comparing samples tested immediately upon loading on the analyzer and samples stored on-board the analyzer for greater than or equal to 3 hours.

iv. The accuracy and precision of the assay were evaluated within-laboratory precision on at least 20 different days and was performed by instrument and reagent lot. The assay demonstrated acceptable precision (repeatability).

v. The reproducibility study demonstrated acceptable precision by reagent lost (across instruments). The within-laboratory precision was estimated using the summation of the repeatability (within-run), between-run, and between-day variance components. And the reproducibility was estimated using the summation of the repeatability (within-run), between-run, between-day, and between-instrument variance components.

vi. The manufacturer has not performed any analytical sensitivity study of the assay arguing that the purpose of this study is to evaluate the analytical sensitivity of the assay when used to test international reference reagents, and currently no external recognized reference material is available. This statement is considered a shortcoming.

vii. Analytical specificity was evaluated referring to potential interfering endogenous substances. The data presented support the use of the assay with specimens that contain up to 20 mg/dL unconjugated or conjugated bilirubin, up to 12 g/dL total protein, up to 3000 mg/dL triglycerides, or up to 500 mg/dL hemoglobin.

viii. In regard to potential interfering exogenous substances, the manufacturer points in the Performance Evaluation Report to have tested the product specific performance characteristics for the several medical conditions unrelated to EBV. Out of 270 specimens that had been tested 3 specimens were found to be discordant and underwent supplemental testing. The data presented support the assay labelling for potential cross reactivities / interferences from patients with diseases unrelated to EBV infection. However, this study has not been developed and included in the analytical performance report (it has been included in the clinical performance report). Experts recommend including it.

ix. The traceability of the assay has been demonstrated through its standardization, ensuring that the assay shows a consistent ability to detect clinically relevant levels of specific analyte so that drift in the assay sensitivity and specificity does not occur over time, especially when implementing successive generations of internal reference preparations.

x. The cut-off has been performed using receiver operating characteristic (ROC) analysis. The data generated during the performance evaluation studies demonstrate that the selected cut-off level (1.00 S/CO) and grayzone range (0.75-0.99 S/CO) are located in the area of optimal combination of sensitivity and specificity. Cut-off was set slightly higher than the maximum of the distance function in order to protect the specificity at an acceptable level of sensitivity. Thus, the assay exhibits the optimum combination of sensitivity and specificity.

xi. The manufacturer has carried out additional studies, such within-assay sample carryover and reagent on board drift. The validity and acceptance criteria were met. The assay is not susceptible to within-assay sample carryover due to the sample pipetter wash settings in the EBV standard

assay files meet the product requirement for within assay sample carryover. Besides, the data supports storage on board of the reagent for a minimum of 30 days.

In conclusion, the analytical performance data demonstrates the state of the art performance of the assay and met all the analytical requirements detailed above, demonstrating that the assay is suitable for the qualitative detection of IgG antibodies to EBV VCA.

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

Clinical performance parameters were determined based on the intended purpose of the device. Additionally, the clinical performance parameters have been assessed against the draft Common Specification requirements. There are currently drafted CS requirements only for Anti-EBV VCA IgG. An assessment against the final Common Specification requirements will be performed and tracked via the post market surveillance process.

The clinical study carried out has evaluated three EBV assays in combination (EBV VCA IgM, EBV VCA IgG, and EBV EBNA-1 IgG) for EBV infection stage determination to maximize sensitivity in the detection of acute primary EBV infection while maintaining high specificity for the detection of a past EBV infection. Therefore, the clinical evaluations for the three assays have been combined into one clinical performance evaluation document in order to allow a comprehensive overview. The Performance Evaluation Report describes the design, conduct and performance results of the assays.

Results from these clinical performance studies were compared with established competitor IVDs. The majority of samples used were prospectively collected. The collections of samples used for determination of clinical sensitivity and clinical specificity and to assess EBV infection stage were adequate in numbers for obtaining statistically relevant results. A high proportion of random clinical samples were included to cover different patient statuses. In addition, commercially available seroconversion panels were used.

The parameters assessed were: within laboratory 5-day precision, relative specificity, relative sensitivity, serum to plasma equivalency (matched serum/plasma), EBV infection stage and other disease states. Results of the device was comparable to an alternative device having similar intended use for all parameters except for within laboratory (total) imprecision and serum to plasma equivalency. Specimens with discrepant results or specimens that were grayzone on any assay underwent confirmation with supplemental testing.

The clinical sensitivity was considered acceptable if the clinical sensitivity point estimate was greater than or equal to the one-sided lower 95% confidence interval of the relative sensitivity of another EBV VCA IgG assay on the same population of EBV VCA IgG reactive specimens. Relative sensitivity reported in the study for EBV VCA IgG was 96.06-97.65%.

The clinical specificity was considered acceptable if the specificity point estimate was greater than or equal to the one-sided lower 95% confidence interval of the relative specificity of another EBV VCA IgG

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

assay on the same population of specimens. Relative specificity reported in the study was 98.35-98.76% excluding grayzone specimens, and 95.83-98.76% across all specimens.

The manufacturer has also evaluated the EBV infection stage using the three assays in combination (EBV VCA IgM, EBV VCA IgG, and EBV EBNA-1 IgG) in order to maximize sensitivity in the detection of acute primary EBV infection while maintaining high specificity for the detection of a past EBV infection. The infection stage determination results for the EBV assay panel and the comparator EBV assay panel were compared to the infection staging results obtained according to the final interpretation (*i.e.* after resolution and confirmation testing using indirect immunofluorescence test, immunoblot and further immunoassay results). The evaluation was based on 1463 specimens. The overall agreement of infection stage determination based on final interpretation assay results compared to the infection stage determination per the EBV assay panel was 95.01% versus 92.28% determined per the comparator EBV assay panel.

The manufacturer has evaluated in the clinical performance report serum to plasma equivalency, demonstrating no performance difference between both types of specimen. All nonreactive or reactive tested plasma specimens showed the same qualitative result on the corresponding serum specimen.

Finally, the manufacturer has carried out a study in order to assess the potential assay interference on specimens from individuals with medical conditions unrelated to EBV infection. The data presented support the assay labelling for potential cross reactivities / interferences from patients with diseases unrelated to EBV infection.

The positive predictive value, negative predictive value and likelihood ratio have been calculated from clinical specificity and clinical sensitivity data. The Positive Predictive Value (PPV), Negative Predictive Value (NPV), Positive Likelihood Ratio (LR+), and Negative Likelihood Ratio (LR-) were generated for the EBV VCA IgG, EBV EBNA-1 IgG, and EBV VCA IgM assays relative to the subject's final status with a combined population of presumed acute infection, random diagnostic, and presumed seronegative specimens.

Regardless, experts identify in this clinical performance report a small number of limitations. No sample used in the clinical performance studies was collected from organ donor centres to prove suitability of the device for determining the EBV immune status of organ donors and recipients. On the other hand, no complementary titre information of positive samples was provided in the evaluation to determine the EBV infection stage. A potential selection bias could occur if these positive samples were not representative of a balanced distribution of low and high titre samples.

In conclusion, clinical performance for the EBV VCA IgG assay has been demonstrated through internal and external evaluations using clinical specimens from patients tested for Epstein-Barr virus in human serum and plasma, and by comparison to existing on market approved assays for the same analyte and intended uses. A review of available data for the EBV VCA IgG assay and other similar products was performed to determine if the product is state of the art in regard to analytical performance and ability to meet its intended purpose, providing medically relevant information necessary for successful patient management. 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 and values reported for these parameters were acceptable.

So, in general, the clinical performance demonstrates that the assay has state of the art performance and is suitable for use as an aid in the diagnosis of infectious mononucleosis, in determining the stage of EBV infection and in determining EBV immune status in organ transplant donors and recipients prior to transplantation.

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's approach to gather the clinical evidence has addressed sufficiently the demonstration of scientific validity, analytical performance, and clinical performance. The manufacturer has provided a Performance Evaluation Plan (PEP) to define the requirements and activities to determine the clinical evidence that supports the intended use in order to demonstrate conformity with the relevant general safety and performance requirements. Scientific validity was based on appropriate literature search and selection. A review of existing literature and available study data was carried out to collect sufficient clinical evidence to establish the use of the Epstein-Barr Virus (EBV) Viral Capsid Antigen (VCA) IgG antibodies for the intended purpose of the device. Evidence of analytical performance was reported for all parameters applicable for a qualitative assay, except analytical sensitivity. Evidence of clinical performance was gathered from four clinical studies using clinical specimens from patients tested for Epstein-Barr virus in human serum and plasma, and by comparison to existing on market approved assays for the same analyte and intended uses. These studies also satisfy the criteria in accordance for state of the art products. It is important to realise that the EBV VCA IgG IVD needs to be performed in conjunction with other serological assays (VCA IgM, EBNA-1 IgG) for clinical interpretation. Clinical evidence sufficiently supports the use of this IVD for intended use.
2. The literature search methodology, protocol and report
The literature search report is clear and extensive. An adequate literature search strategy is implemented for screening relevant publications as well as clearly defined inclusion and exclusion criteria for selecting those most consistent methodologically. The manufacturer has developed a suitable literature search methodology and has compiled 32 publications to support the scientific validity of the assay. After applying inclusion and exclusion criteria, the manufacturer has excluded 24 articles and only has included 8 articles for the report. Given

the intended use of the device, this was appropriate. However, a more detailed review of a more comprehensive set of references may be advantageous.

The databases used for this search are acceptable because they include favorable and unfavorable data, are easily searchable, and contain biomedical articles. Additionally, the databases index a large number of journals from different geographical locations. The time frame chosen for the initial article search is used to obtain the most current information on recent research using current products. The search strategies designed for the manufacturer ensure both positive and negative product study outcomes and are included in the reports.

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 assay is based consists in an automated two-step immunoassay for the qualitative detection of IgG antibodies to EBV VCA in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology. This CMIA assay uses peptide-coated microparticles (VCA p18) and acridine-labelled anti-IgG conjugates for qualitatively detecting VCA IgG antibodies. The chemiluminescent signal is measured by a photomultiplier tube and expressed as relative light units (RLU) and samples are processed on a fully automated random-access analyser.

Indirect immunofluorescence (IIF) assays have historically been considered the gold standard for EBV antibody testing, despite the fact that the reading of the assay results is subjective. However, although immunofluorescence assays are considered to be more specific than enzyme immunoassays (EIAs), their sensitivities have occasionally been reported to be lower than those of EIAs, especially for VCA IgM and VCA IgG antibody detection.

The key advantages of chemiluminescent analytical methods reside in the wide dynamic range, high signal intensity, absence of interfering emissions (high specificity), rapid acquisition of the analytical signal, high stability of reagents and their conjugates, low consumption of reagents, random access, reduced incubation time and full compatibility with immunology assay protocols. Currently, the prevailing technology is the CMIA technology and compares favorably with immunofluorescence, the recognized gold standard. Other technologies such as PCR or CLIA yield results equal to but not superior to the CMIA products.

The intended purpose of the device is the qualitative detection of IgG antibodies to Epstein-Barr Virus (EBV) Viral Capsid Antigen (VCA). The information intended to be provided is based in the combination of three markers (Anti-EBV-VCA IgM, Anti-EBV-VCA IgG, Anti-EBNA-1 IgG), resulting firstly in an aid in the diagnosis of infectious mononucleosis and in determining the stage of EBV infection (acute vs. past infection), and secondly in determination of EBV immune status in organ transplant donors and recipients prior to transplantation.

The device is an automated qualitative assay intended to test in individuals suspected to have acute mononucleosis and in potential organ donors / organ recipients. The device is intended to use for laboratory professional only.

The general safety and performance characteristics are based on the intended purpose of the device and are maintained throughout the product lifecycle. Specifications are described in the Analytical Performance Requirements and Clinical Performance Requirements sections of the Performance Evaluation Plan.

The manufacturer assures that risk assessment will be conducted over the lifecycle of the device per the risk management plan. It is supposed that risk analysis will be performed and include user needs, product requirements and associated performance criteria as potential sources of hazardous situations. The manufacturer claims that risk acceptability criteria are defined in the risk management plan and residual risk is assessed against the risk acceptability criteria. Besides, the manufacturer states that a benefit risk assessment will be performed to assess whether the benefits of the device outweigh the risk, and that residual risk and benefit risk will be documented in the risk management report. However, the manufacturer has not included the risk management plan or the risk management report in the dossier to check it.

The manufacturer has designed, protected and labelled the product as control measures, in an effort to mitigate any residual risks. These measures are in place to minimize all aspects of misuse, safety and result integrity and that is because users are informed about significant residual risks through the labelling (*i.e.*, package insert) of the device.

The manufacturer assures that overall risk profile for the assay, including all risk levels and labelling only control measures, was carefully evaluated against the benefit of the device and it was concluded that the medical benefits of the intended use outweigh the overall residual risk.

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

The assay is intended to be used as an IVD assay. State of the Art should be assessed for the assays with the same intended purpose as this device.

The specific determination that the assay is a state of the art product is made considering, but not limited to, the following factors:

- The assay has showed in patient samples to have a minimal within laboratory imprecision and maximum relative specificity and sensitivity comparing to another assay on the same population of specimens. Minimal interference has been observed with elevated unconjugated bilirubin/conjugated bilirubin, triglycerides, protein, or hemoglobin within normal physiological ranges, and has displayed lack of cross reactivity with other disease states as well.
- The assay has demonstrated to be a system that is efficient, and has high throughput to evaluate many samples per day. In addition, the assay has showed low cross reactivity and lack of interference. These points are critical features for an effective state of the art product.
- Similar assays for EBV VCA IgG have been evaluated against this assay for analytical and end user features in alignment with the intended purpose. The manufacturer has made a comparison of assays with other two generations of the device based in chemiluminescent microparticle immunoassays (CMIA), and with other similar devices based on PCR, chemiluminescent

immunoassay (CLIA), a 2-step enzyme immunoassay sandwich method with a final fluorescent detection (ELFA) and a multiplex flow immunoassay. The final product analytical performance is consistent with competitive on market products.

- State of the Art (SoA) Report includes two studies. In the first one, the assay is established State of the Art for a seroprevalence study due to its high throughput capacity required for this task. In the second one, the study concluded that the assay serology panel provided good sensitivities and specificities for EBV serostatus determination prior to transplantation and consistent with the needs of the state of the art for this project as defined above.

The clinical evidence supports the use of this IVD for intended purpose, however the utilization of organ donor samples for evaluation of clinical performed is not stated in the PER and experts think clinical samples are insufficiently characterized. This report would be enriched with that type of samples.

In conclusion, the evidence included and summarized in this report supports the use of the EBV VCA IgG marker in clinical applications as an aid in the diagnosis of infectious mononucleosis and in determining the stage of EBV infection and EBV immune status in organ transplant donors and recipients prior to transplantation. Based on the relevant consolidated findings of science, technology and experience as it relates to this device, this review defines the generally acknowledged state of the art relative to what is currently and generally accepted as good practice in technology and medicine for this analyte.

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

The manufacturer has developed a Post Market Performance Follow-up (PMPF) Plan in order to confirm the safety, performance and scientific validity throughout the expected lifetime of the device, to ensure the continued acceptability of the benefit-risk ratio and to detect emerging risks on the basis of factual evidence.

The PMPF evaluation report is targeted for completion in Q4/2022. The manufacturer describes in the PMPF Plan the activities which will be carried out at the time of the PMPF Report. These activities include:

- Evaluate for any changes to Scientific Validity Report (SVR) developing an updated literature review which will cover the time period from the latest SVR update to the time of the PMPF Report. Assessment and gap-analysis of draft common specifications to the final common specifications.
- Assessment of State of the Art (SoA) evaluating any update in the common specification or harmonized standards for the device and reviewing literature to re-assess current thinking in medical practice.
- Evaluate any analytical and clinical performance changes through an updated literature review ensuring that the parameters associated with the analytical and clinical performance are still applicable to the device and do not need to be updated.

- Identify any performance issues and new risks associated or potential misuse of the device through customer feedback and complaints reports and reviews updates made to Product Risk Analysis and Risk Management Report, ensuring there are no deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the device after its release for sale or distribution.

In conclusion, the PMPF Plan and the monitoring activities included are appropriate for post-market performance follow-up and ensure safe performance of the assay in operational conditions.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report

The description of the state of the art and the scientific validity, analytical, and the clinical performance evidence gathered for this device demonstrates that the EBV VCA IgG assay is safe and performs effectively when used according to its intended purpose.

The assay is an automated chemiluminescent microparticle immunoassay (CMIA) for the qualitative detection of IgG antibodies to Epstein-Barr Virus (EBV) Viral Capsid Antigen (VCA) in human serum and plasma. The device is intended to be used by professional users that receive specialized product training. The benefits are to aid in the diagnosis of infectious mononucleosis and in determining the stage of EBV infection and EBV immune status in organ transplant donors and recipients prior to transplantation.

Generally, the experts were positive about the content and extent of the submitted dossier. However, there are several recommendations for evaluation of the assay and for improvement of the dossier:

- The manufacturer has not performed any analytical sensitivity study of the assay arguing that currently no external recognized reference material is available. The analytical performance report must include any analytical sensitivity study, *e.g.* by use of a well-characterized reference preparation (*e.g.* NIBSC) and characterisation in the CMIA assay and comparator assays.
- Inclusion of samples collected from organ donors and recipients in the clinical performance studies.
- The manufacturer has made a good Post Market Performance Follow-up (PMPF) Plan to ensure the continued acceptability of the benefit-risk ratio and to detect emerging risks on the basis of actual evidence. However, the manufacturer has not included the Risk Analysis, the Risk Management Plan and the Risk Management Report in the dossier.

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 views.

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

[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.