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	19/10/2021
Notified Body Number	0123
Internal PECP dossier #	IVD-2021-000007
In vitro diagnostic medical device	The device is a qualitative double-antigen sandwich assay for the detection of Antibodies to SARS-CoV-2 in serum/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)*	Antibodies (including IgG) to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
P2	function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc*	Aid in the determination of the immune reaction to SARS-CoV-2.
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.*	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
P4	whether it is automated or not	Fully automated
P5	whether it is qualitative, semi-quantitative or quantitative	Qualitative
P6	type of specimen(s) *e.g. whole blood, serum, saliva etc*	Serum, venous plasma
P7	where applicable, the testing population *e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range*	No specific testing population
P8	intended user	Professional Laboratory User
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.*	Double-antigen sandwich assay using electro-chemi-luminescence detection method (ECLIA)

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group

Date of views	14/12/2021
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-7

3.2 Summary of expert panel views

The proposed assay is an *in vitro* anti-SARS-CoV-2 assay directed against the nucleocapsid protein. The technology is commonly used by the manufacturer. The assay is a one-step double-antigen sandwich assay which runs on fully automated systems, with results being available within 18 minutes. The assay is used to support diagnostics of COVID-19 infections, for epidemiological purposes and for the identification of specific groups at a higher risk of infection. The assay cannot be used to identify vaccinated individuals vaccinated with envelop antigens. The detection of IgM/IgG antibodies can also be supplementary to identify infections who are PCR negative.

The assay is already on the European market under the *In Vitro* Diagnostic Directive 98/79/EC. The supported Performance Evaluation Report (PER) document, describes the characteristics and performance of the assay according to the requirements mentioned in the Performance Evaluation Report.
However, the scientific literature could be updated with also a focus on comparison with data from competitive CE-IVD assays.

The approach by the manufacturer is in line with current state-of-the-art technologies. The approach chosen by the manufacturer is straightforward and already in use. However, the information on scientific validity and the use of different clinical materials, like different plasma formulations, for the detection of antibodies against the SARS-CoV-2, could be updated.

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

Views of the expert panel on the performance evaluation report of the manufacturer (PER)
1. Expert views on the scientific validity report[1]
The use of antibody assays directed against the nucleocapsid protein of SARS-CoV-2 are useful in several specific situations, like determining specific groups at high risk of infections, for viral epidemiology or to support diagnostics of COVID-19. The protocol follows the guidelines as described in Annex XIII (part A, 1.2) of EU Regulation 2017/746 to critically evaluate the validity of the measurement of antibodies to SARS-CoV-2 for its clinical intended purpose. The literature review supporting the scientific validity was carried out according to the procedure described in the IVDR Literature Search and Selection Protocol and Report using the online PubMed database service, clinical practice guidelines (e.g., Centers for Disease Control and Prevention [CDC], European Centre for Disease Prevention and Control [ECDC], World Health Organization [WHO]. The data provided are from January 4, 2021. No update after this date was further analysed. Also no comparison of the assay with other CE-IVD assays on the marker was identified.
2. Expert views on the analytical performance report[2]
Data on the analytical performance of the assay are provided in Table 1 as well in the Elecsys Anti-SARS-CoV-2 method sheet. Mentioned are the information that no interference of the assay was observed on several listed endogenous substances, on seventeen commonly used pharmaceutical substances (at 5-times the daily dosage) and a list of special drugs. Samples were tested up to 120 COI. The precision of the assay was established on different platforms used by the manufacturer, with a selection of human serum samples, who were classified as negative, low positive, positive as well as negative near the cut-off of the assay. Repeatability and intermediate precision were established for the different categories mentioned before. Data on serum samples were only determined; no data on different plasma samples were provided, like the use of Li-heparin, K_2-EDTA and K_3-EDTA plasma. It was also mentioned that heat-inactivated samples should not be used. The device reports results in a semiquantitative manner as cut-off index (COI) values, with COI>1 being reactive, COI<1 non-reactive. A WHO International Standard for anti-SARS-CoV-2 has been established with an assigned unitage (IU/ml) for neutralization activity and proposed units for binding antibodies (BAU/ml). This preparation originated from a convalescent plasma and thus covers different antibody targets (e.g. anti-S, anti-N) reflecting different antibody classes (e.g. IgG, IgA, IgM). Its potential use for calibration of an assay detecting different measurands (here: different antibody classes) is

[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

scientifically not justified, therefore traceability to a reference preparation of higher order is currently not possible. This rationale is not provided in the Performance Evaluation Report obtained by the manufacturer.

Finally, no comparison with other CE-IVD assays on the market was performed.

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

Data on the clinical performance of the assay are documented in Table 2.

The general assumption is that serological assays can detect seroconversion after an infection, like with the SARS-CoV-2 virus, after two weeks for total antibodies, with initial detection of IgM antibodies after the onset of symptoms.

The current assay was developed in a time that no vaccination was available, and because all current vaccines used in Europe are directed against the surface or spike, protein, the assay is unable to detect a response to vaccination because it is directed against the nucleocapsid protein. This may change of course with the availability of other vaccines.

The clinical sensitivity of the assay was set with acceptance criteria to be above or equal to 90% for samples taken >21 days after the onset of symptoms. The overall sensitivity including the detection of an early infection should also be comparable to other CE-marked assays. The data on the overall sensitivity including early infection is not exactly known. The samples analyzed (496 in total, see leaflet VV-174063 V5.0) were taken before and after these 14 days post PCR confirmation from 102 symptomatic patients. Also samples from asymptomatic, subclinical and mildly infections were analysed, although the clinical data are not shown. These 496 positive specimens did not include samples from vaccinated individuals; the assay was developed in a period that vaccination was not available.

The clinical sensitivity was determined in relation to the time period after PCR confirmation, which is not always very accurate. The data shown in Table 2 were divided into three groups by “days post PCR confirmation”. The data show a sensitivity of 60.2% within 0-6 days after PCR positivity, 85.3% after 7-13 days after PCR positivity, and 99.5% after 14 days of PCR positivity. These data are in line with the expectations defined in the “Guidance on performance evaluation of SARS-CoV-*2 in vitro* diagnostic medical devices (MDCG 2021-21)”. In conclusion, the threshold set at a clinical sensitivity of more than 90% for samples taken at 21 days or later was met, because the result was 99.5% after 14 days after a confirmed PCR positivity.

Data on the sensitivity in relation to the differect Variants of Concern (VoC) are limited. It is mentioned that no impact on the assay performance was detected in testing samples from patients infected with alpha B.1.1.7 and beta B.1.351, but data or the number of samples tested are not shown.

Diagnostic specificity is determined from the analysis of 400 samples from non-infected and non-vaccinated individuals and estimated to be above 99% in this population. The samples were obtained from a period before December 2019, when the pandemic has not started yet.

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

Data from 200 hospitalized patients are not clearly described, but from the analysis of interfering and cross-reacting blood specimens, it can be concluded that acute infection of EBV and CMV, as determined by IgM and IgG antibodies, as well as systemic lupus erythematosus, could be interfering resulting in less specificity of 98.1%, 98.8% and 90%, respectively. From 792 samples tested for cross-reactivity, an overall specificity was determined of above 99%, with the infections mentioned before as cross-reacting.

The specificity data provided are in line with expectations defined in the "Guidance on performance evaluation of SARS-CoV-2 *in vitro* diagnostic medical devices (MDCG 2021-21)".

3.4 Views on specific assessment aspects of the performance evaluation report (PER)

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 clinical evidence based on scientific validity, analytical performance, and clinical performance data. The performance requirements follow the Annex I of Regulation (EU) 2017/746. The data presented in this report indicate that the device and assay will achieve its clinical benefit. The clinical benefit of the IVD is to measure antibodies to SARS-CoV-2 in human plasma and serum, although the data presented *only* refer to data in serum. Since the assay specifically detects antibodies directed against the nucleocapsid, the assay cannot be used for detecting immune response after vaccination with a vaccine containing NOT the nucleocapsid. However, at the time being the assay may be of use for detecting natural SARS-CoV-2 infections, including break-through infections after vaccination. The performance of the assay was validated with leftover native samples collected either from diagnostic routine (German population) or blood screening routine (US American population). These samples were from pre-pandemic cohorts to establish the specificity of the assay. Specificity of the assay was above 99%. For sensitivity testing, seroconversion samples from donors without the need of hospitalization as well as sequential, anonymized leftover samples from patients with hospitalization after PCR-confirmed SARS-CoV-2 infection (both from German population) were analysed. These data are shown in Table 2. The sensitivity of the assay is respectively 60.2% after 0-6 days post PCR confirmation, 85.3% after 7-13 days post PCR confirmation, and 99.5% after more than 14 days post PCR confirmation. The evidence provided is adequate to demonstrate the intended use of the method.
2. The literature search methodology, protocol and report
There has been a literature search following the guidelines as described in Annex XIII of the EU regulation 2017/746 and documented in SOP RP0083. The outcome of this research is not made

available. Search items were used on January 4th, 2021, in the PubMed database with appropriate filters. The conclusion at that time were a selection of 147 potentially relevant articles of which 54 articles were used as reference in the Scientific Validity Report. Also this report is not attached.

Looking at more recent literature search (28th November 2021) in PubMed with the search items ECLIA & COVID &2021, already identified 37 published papers. Looking at a selection of these indicates that the performance of the assay is favourable, and no controverting findings could be identified.

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 is a fully automated, qualitative, one-step double-antigen sandwich assay. The recombinant protein antigen used is representing the nucleocapsid (N) antigen and is full-length. The assay uses the two antigens labelled with Biotin and Rhutenium-complex respectively. The labelled antigen is presented in such a way that it predominantly captures anti-SARS-CoV-2 IgG, but also anti-SARS-CoV-2 IgA and mature anti-SARS-CoV-2 IgM. Results can be achieved within 18 minutes. At this moment of time, it is still under investigation whether the current Delta or Omicron variant, can be detected with the same efficiency. However, since these variants are characterized by mutations in the S-gene, a direct impact on the assay's efficiency is not expected.

The intended purpose of the assay is to identify individuals who have been infected with the SARS-CoV-2 virus, and specifically not for detecting a response after vaccination. The assay is intended as an aid in determining the immune reaction to SARS-CoV-2, meaning more specifically antibodies IgG, although IgM and IgA antibodies can also be detected. Other supportive diagnostic assays are available like the detection of the virus by the PCR method.

A Product Risk Assessment was carried including a Medical Risk Assessment (not attached). This has examined all possible sources of risk with the conclusion that any foreseeable risks and any undesirable effects of the product have been minimized. The risk management process follows ISO 14971:2019 and is applied during the entire lifetime of the product. The conclusion by the manufacturer states that the overall risk is acceptable, and the product has potential benefits for patients. Documents are not attached.

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

The clinical evidence of the method has been described before, but only data from serum samples were provided. Furthermore, acceptance criteria for exogenous substances were established (see Table 2), both for endogenous substances and pharmaceutical substances.

Furthermore, the analytical specificity against potentially interfering and cross-reacting blood specimens were described, as well as against other pathogens of respiratory diseases. Specificity was 100% except again acute CMV IgM/IgG (98.8%), acute EBD (IgM/IgG) 98.1% and SLE (90%). The overall specificity in this study was 99.5% out of 792 samples analysed.

The clinical evidence provided and presented in Table 2 shows data on specificity, sensitivity, and interfering substances. Together with the 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.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report
The information provided by the manufacturer is a comprehensive summary covering the main aspects of the Performance Evaluation Report. The data provided gives an overview on the analytical sensitivity and specificity and the clinical value of the assay for the intended purpose. The technology is state-of-the art. The information provided by the manufacturer shows its principal compliance with the IVDR requirements. However, direct comparison of the assay with other state-of-the-art assays is missing, potentially explained by development of the assay already at an early stage of the SARS-CoV-2 pandemic. It would be recommended to provide an update search of the literature, including publications on direct comparison of the assay with competitor assays. There are additional recommendations for the manufacturer to provide evidence for its use in plasma samples. The ability to detect antibodies raised against new variants of concern of SARS-CoV-2 should be continuously checked and updated information made available.

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.
Not relevant

[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
There were no divergent views.

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

[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.