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	24/11/2021
Notified Body number	0123
Internal PECP dossier #	IVD-2021-000013
***In vitro* diagnostic medical device**	Chemiluminescent microparticle immunoassay (CMIA) used for the qualitative and quantitative determination of IgG antibodies to SARSCoV-2 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)		
P1	what is detected and/or measured *please specify the analyte(s) or marker(s), e.g. SARS-CoV-2 spike protein, Kel1 (K)*	Determination of IgG antibodies to 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 diagnosis of SARS CoV-2 infection • aid in evaluating immune status of infected individuals • to monitor antibody response in individuals that have received the COVID-19 vaccine
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.*	Exposure to SARS-CoV-2 or SARS CoV-2 vaccination control
P4	whether it is automated or not	automated
P5	whether it is qualitative, semi-quantitative or quantitative	qualitative and quantitative
P6	type of specimen(s) *e.g. whole blood, serum, saliva etc*	Human serum and plasma
P7	where applicable, the testing population	Individuals who are suspected to have had coronavirus disease (COVID-19) or

	e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range	individuals that may have been infected by SARSCoV-2 or have been vaccinated against SARS-CoV-2
P8	intended user	For Laboratory Professional Use Only
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.*	Chemiluminescent microparticle immunoassay (CMIA) technology

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group

Date of views	04/02/2022
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-13

3.2 Summary of expert panel views

The test is designed for the quantitative and qualitative determination of SARS-CoV-2 of IgG antibodies against the receptor binding domain (RBD) in human serum and plasma. It is an indirect test principle (anti-human IgG) on an established and well-known device. The cutoff value is 50 Arbitrary Units per ml (AU/ml) and is calibrated to the applicable WHO international standard (NIBSC 20/136). The method is automated and should be used by laboratory professionals. The target populations involve: (i) in general, as an aid in the diagnosis of SARS-CoV-2 infection, (ii) aid in evaluating immune status of infected individuals, and (iii) to monitor antibody response after vaccination. The test should be used in conjunction with clinical presentation and other laboratory tests

Test principle, test technology and test platform are well known and accepted. New under the IVDR is the application to the specific marker SARS-CoV-2 antibody detection

For this purpose, the manufacturer has submitted a comprehensive dossier.
The dossier includes the requirements of Annex I and II of the IVDR and follows the MDCG guideline for diagnostic testing of SARS-CoV-2, which is expected to be the final Common Specifications (CS) for the performance evaluation of SARS-CoV-2 tests.
Therefore, the approach presented by the manufacturer to demonstrate the clinical evidence by the manufacturer is appropriate and acceptable.

There are three points that need to be clarified and which are also not entirely consistent with the above-mentioned CS guidance: (i) Determination of the sensitivity of the test for SARS-CoV-2 IgG for a longer duration, since it is known that SARS-CoV-2 IgG decreases over time, and sensitivity shown so far covers practically only a short period of one month after symptom onset. (ii) Influence of Covid-19 severity level on the antibody level and sensitivity (test-positivity). (iii) In addition, it is noted that the one claim of the test for determining immune protection and correlation with neutralization refers to the current Covid-19 vaccine based on Wuhan virus, which may not be the case for new variants in the future. For the test itself, it is not described from which virus or variant the RBD antigen is derived. Also, data on other variants should be further evaluated.

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 manufacturer demonstrates the scientific validity based on the following sources: • information on other devices measuring the same marker in a State of the Art (SoA) Report. • scientific (peer-reviewed) literature; There are 104 publications mentioned. The conclusion of the manufacturer derived from the scientific validity were rather general: “The evidence included and summarized in this report supports the use of SARS-CoV-2 IgG II Quant assay in clinical applications as an aid in the diagnosis of SARS-CoV-2 infection in conjunction with clinical presentation and other laboratory tests, and also as an aid in evaluating immune status of individuals that have received the COVID-19 vaccine, by quantitatively measuring IgG antibodies against the spike receptor-binding domain (RBD) of SARS-CoV-2.” The following comments are made. Intended use claim 1: “Aid in the diagnosis of SARS-CoV-2 infection in conjunction with clinical presentation and other laboratory tests.” The performance data to date shows only a relatively short period for detection of only up to about one month. A related limitation of the test is that antibodies may decrease over time and results become negative or below the threshold of the assay. Therefore, the scientific validity does not adequately address declining and detection of IgG antibodies by the test over time. Since titers and sensitivity of IgG SARS-CoV-2 antibodies are time dependent, this should be clarified. Intended use claim 2: “Aid in the evaluation of immune status of infected individuals and to monitor antibody response in individuals that have received the COVID-19 vaccine.” Claim 2 is considered more a non-class D claim, i.e., class C, and therefore may be out of scope here. Regarding the claim that the test correlates with immune protection, it should be noted that immune protection depends on several parameters which were not validated by this test.

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

2. Expert views on the analytical performance report[2]
A detailed analytical performance report was provided. The analytical testing parameters required by the IVDR were evaluated. From the data provided, it shows that all analytical parameters of the test were performed according to specifications and were within the acceptance criteria. The analytical performance of the product is in line with relevant competitive products on the market from other manufacturers in terms of analytical characteristics such as analytical sensitivity, analytical specificity, precision, accuracy, cross-reactivity and potential interferences. The automated instrument, as well as its required accessories specific to the intended end-user environment, is also functional consistent with similar competitive products. These analytical parameters are important for the proper execution of the test. There were no outstanding issues. As mentioned above, the test technology, the platform, and the instrument are well known and proven; there are no specific new issues and no further comments to add.
3. Expert views on the clinical performance report[3]
A comprehensive clinical performance evaluation report was provided by the manufacturer. The clinical evaluation followed closely the applicable SARS-CoV-2 guidance, which is intended to be the final CS. The clinical evaluation approach chosen is therefore adequate. 2008 pre-pandemic specimens from blood donors and hospitalized patients (collected prior to September 2019) were used for specificity determination. Overall specificity of the product was shown to be 99.6% in this population. Cross reactivity was evaluated on a series of 251 samples from 49 different disease states relevant for differential diagnosis and showed 100% specificity. Overall assay precision across the measuring interval was determined to be < 6% CV. Sensitivity for 80 specimens collected >15 days post symptom onset was 99.4%. Adequate sensitivity was also found in 359 specimens for days ≤ 7 and days 8-14 after symptom onset. In a study with seroconverting samples, the sensitivity was determined. The acceptance criteria of the CS guidance on SARS-CoV-2 Tests were mostly met, except for the points commented above under section 3.2.

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 in providing clinical evidence is based on the required provisions of the IVDR 2017/746 and the CS on SARS-CoV-2 antibody testing (MDCG-2021), which is available as a guidance and represent the draft of the expected final CS.

[2] Annex XIII, Section 1.2.2 of Regulation (EU) 2017/746 - Demonstration of the analytical performance
[3] Annex XIII, Section 1.2.3 of Regulation (EU) 2017/746 - Demonstration of the clinical performance

Thus, the implemented evaluation approach, e.g. sample size, specimen characterization, acceptance criteria were adequate.

2. The literature search methodology, protocol and report

The literature search is extensive and adequate. However, the relevance of this literature search regarding the time limitation of IgG-RBD detection and the dependence on Covid-19 symptoms, which is important for sensitivity, was not sufficiently apparent.
The literature search comprises only the period until March 2021. A search beyond that time would likely yielded more findings, based on the rapidly increasing scientific knowledge on SARS-CoV-2.

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 of the test is the detection of RBD-specific SARS-CoV-2 antibodies of the IgG class by an indirect assay design (anti-human IgG conjugate labeled with acridinium).
This assay principle has been known for a long time and corresponds to the state of the art for the determination of IgG antibodies. Therefore, the technology can be considered suitable for the detection of SARS-CoV-2 IgG antibodies, as also demonstrated in the scientific validity report and literature search.

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

The approach for clinical evaluation is in general acceptable. The test was evaluated in comparison to other tests for the same intended use.

As mentioned above, the CS guidance was followed. However, the CS were not completely fulfilled in the following points: The CS guidance requires that sensitivity samples should include individuals from different time courses, in the early stage of infection and after seroconversion (within the first 21 days and after 21 days of symptom onset); and also samples from asymptomatic or subclinical patients and individuals with mild symptoms (ambulatory). The background is that sensitivity may be variable in the early infection period and decreases over time. Also, patients with mild Covid-19 disease and asymptomatic individuals are associated with lower antibody titers and lower sensitivity. Considering this, the evidence of how the test sensitivity performs over a longer time course and with different levels of Covid-19 disease in those patients, is not yet fully determined.
The following is noted in relation to the claim for quantification of antibodies and possible correlation to immune protection. The performance evaluation, as far as evident from the data presented, refers to the alpha variant. The manufacturer has not described from which variant the antigens are derived from, and used for the test. Thus, it is not clear how the quantitative sensitivity and the claimed correlation with neutralization are affected by different variants. It therefore seems appropriate to consider the performance of the test with respect to the emergence of new variants, e.g. Omicron.

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

A PMPF was not available, only a PMPF plan.

Data from PMS would be helpful to update the clinical benefit of the test regarding the comments to the performance evaluation.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report
Overall, the general approach presented for the performance evaluation of this test is acceptable and essentially consistent with the current SARS-CoV-2 guideline, which is expected to be the final CS. However, the CS guideline has not yet been fully followed with respect to demonstrating sensitivity: For sample selection to include asymptomatic and mild Covid-19, and it is not adequately clarified how sensitivity will result over a longer period of time post-infection than shown so far, as SARS-CoV-2 IgG detection is mainly used for past infections. It is recommended that further data or additional clarification on this should be requested.

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.

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**

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

[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.