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-2021-000012
***In vitro* diagnostic medical device**	Chemiluminescent microparticle immunoassay (CMIA) used for the qualitative detection of IgM antibodies to SARS-CoV-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 IgM 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
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
P4	whether it is automated or not	automated
P5	whether it is qualitative, semi-quantitative or quantitative	qualitative
P6	type of specimen(s) *e.g. whole blood, serum, saliva etc*	Human serum and plasma
P7	where applicable, the testing population	Individuals who are suspected to have had coronavirus disease

	e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range	(COVID-19) or individuals that may have been infected by SARSCoV-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	03/02/2022
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-12

3.2 Summary of expert panel views

Device description:
"The SARS-CoV-2 IgM assay is a chemiluminescent microparticle immunoassay (CMIA) used for the qualitative detection of IgM antibodies to SARS-CoV-2 in human serum and plasma. The SARS-CoV-2 IgM assay is to be used as an aid in the diagnosis of SARS-CoV-2 infection in conjunction with clinical presentation and other laboratory tests. Results from the SARS-CoV-2 IgM assay should not be used as the sole basis for diagnosis."
The target population are serum or plasma from individuals who are suspected to have a current or recent or recurrent coronavirus disease (Covid-19) or in individuals that may have a current, a recent or a recurrent infection by SARS-CoV-2.
The assay is an indirect test assay (anti-human IgM). The measuring principle is a chemiluminescent microparticle immunoassay (CMIA). Instrument-based on well-known platform. The cutoff is defined qualitatively by the "sample to cutoff ratio".

View of the expert on the test design and technology:
Test principle, test technology and test platform as such have no novel features. New under the IVDR is its application to the specific marker SARS-CoV-2 antibody IgM detection.
View of the expert on the performance evaluation report:
The performance evaluation study submitted by the manufacturer follows the requirements of the IVDR and the MDCG Guidance for diagnostic testing for SARS-CoV-2. Most performance parameters

appear to have been evaluated sufficiently well. Some requirements of the CS guideline related to sensitivity, though, have not yet been fully addressed: The detection duration of anti-SARS-CoV-2 IgM with the test after the seroconversion phase has not been elaborated sufficiently. On the other hand, IgM detection is known to decrease rapidly after 30 days. It was not described from which patients or subjects the sensitivity was determined. However it is known that the sensitivity of SARS-CoV-2 antibody tests significantly correlates with the severity of Covid-19. The possible influence of SARS-CoV-2 variants was not addressed. In this regard, it is noted that it might be useful to describe the target antigen used by the test in more detail, e.g., S1 or whole spike, for example. It was not specified whether the test is suitable for vaccinated individuals. According to the instructions for use the test do not seem to preclude this.

Views on the adequacy of the approach chosen by the manufacturer:
The approach chosen for the performance evaluation study follows the CS guidance, which is expected to become the final Common Specifications (CS) for performance evaluation of SARS-CoV-2 tests, which is acceptable.

Overall conclusions and recommendations on the performance evaluation report:
The performance evaluation provided by the manufacturer was essentially acceptable, however, as mentioned above, some questions remained regarding the sensitivity of the test. First, some sensitivity requirements of the CS guidance were not fully addressed. In addition, the intended use of the test was rather general, and not all thereby involved claims were fully supported by the performance assessment data presented. These issues are also important for the appropriate use of SARS-CoV-2 antibody diagnostics according to the current medical state of the art. Providing more data on performance in individuals infected with other Variants of Concern should be added; data on individuals infected with the current dominant and expanding Omikron variant would be recommended.

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 report. Scientific (peer-reviewed) literature; 47 publications were included. The conclusion of the manufacturer derived from the scientific validity were held rather general: “The evidence included and summarized in this report supports the use of the SARS-CoV-2 IgM marker in clinical applications as an aid in the diagnosis of SARS-CoV-2 infection in conjunction with clinical presentation and other laboratory tests. Based on the relevant consolidated findings of science,

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

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. Summary of the state-of-the-art is that the SARS-CoV-2 IgM product conforms to expectations currently. The next applications may consider Total Ig or utilizing a combination of antigen targets for higher sensitivity."
Overall, the state-of-the-art was presented. The test was compared with other relevant tests and a comparison with assays from competitor manufacturers. However, the state-of-the-art report and literature search do not address the basic questions raised above in section 3.2.

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 appears 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 consistent with similar competitive products. These analytical parameters are important for the proper carrying out of test. There were no outstanding issues. Since as mentioned above, the test technology, platform, and instrument are well known and proven, there were no specific new points and no additional comments.

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

A comprehensive clinical performance evaluation report was provided. The clinical evaluation followed closely the applicable SARS-CoV-2 guidance, which is intended to be the final CS. The clinical evaluation approach chosen therefore adequate. 2965 pre-pandemic specimens from blood donors and hospitalized patients (collected prior to September 2019) were used for specificity determination. Thirteen were reacting positive. Overall specificity of the product was shown to be 99.6% in this retrospectively assessed specimens. Two out of 208 samples from patients with forty-nine different diseases considered for differential diagnosis and showed cross-reactivity in this test. A patient sample with elevated rheumatoid factor and a sample from a hemodialysis patient show a false positive reaction. Overall assay precision across the measuring interval was determined to be < 6% CV. Sensitivity was determined using 326 samples: 92 <= 7 days, 126 samples 8-14 days, 90 samples 15-30 days, and 18 samples ≥31 days after symptom onset. Sensitivity was 46.7%, 85.7%, 96.7%, and 100%, respectively. In a study of eleven longitudinal samples from 2 subjects, seroconversion sensitivity was determined, and the test was positive at 7 or 10 days.

Not fully clarified was the sensitivity over the period after seroconversion. There was a small footnote from the manufacturer that the duration of the IgM antibody response has not been fully characterized. On the other hand, it is known that IgM detection decreases rapidly after 30 days.

[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

There was no description from the patient population involved of the samples tested in terms of severity of Covid-19, and it is not clear whether mildly diseased and asymptomatic individuals were included, which represent the majority, resulting in patient spectrum bias. Given the correlation between the sensitivity of SARS-CoV-2 antibody tests and the severity of Covid-19, this would be important to clarify.

Potential cross-reactivity with the four known endemic human coronaviruses (HKU1, NL63, OC43, or 229E) was not explicitly investigated by the manufacturer. This is not entirely consistent with CS guidelines. On the other hand, no cross-reactivity was observed in a patient population with respiratory diseases other than Covid-19, including viruses relevant to differential diagnosis, and no non-specificity was observed. In addition, specificity was evaluated with a larger number (2965) of samples than required (200), achieving a high specificity of 99.6%. Since cross-reactivity can be considered as part of the total specificity and substantially more samples were tested for both diagnostic and analytical specificity, this can be accepted. This is also because the current medical state of the art does not indicate significant cross-reactivity between antibodies against SARS-CoV-2 and the known endemic human coronaviruses.

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 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. Thus, the implemented evaluation approach, including sample size, specimen characterization and acceptance criteria were adequate.
2. The literature search methodology, protocol and report
The literature search is extensive and comprehensible according to defined search criteria. However, the relevance of this literature search regarding the detection duration of IgM-Spike detection and the dependence on Covid-19 symptoms, which is important for sensitivity, was not sufficiently apparent. The literature search comprises the period until April 2021. An updated search would yield further relevant findings, as is to be expected based on the rapidly developing 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 Spike-specific SARS-CoV-2 antibodies of the IgM class by an indirect assay design (anti-human IgM 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 IgM

antibodies. Therefore, the technology can be considered suitable for the detection of SARS-CoV-2 IgM antibodies.

The intended use is very general, with no further breakdown for a particular stage of infection or target group. This requires a correspondingly broad performance evaluation covering all possible claims. However, the data presented so far do not support this wide range of performance. Also, the limitations of the test in the instructions for use is not defined.

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

The approach to clinical evaluation chosen by the company is acceptable. The requirements of the IVDR and of the applicable MDCG-2021 CS guidance on the evaluation of SARS-CoV-2 tests were followed. The test was compared with other tests for the same intended use.

However, the CS were not fully met for the sensitivity evaluation at some points. The issues that arose also concerns the appropriate use of the test based on current medical state-of-the-art.

The points in detail:

The CS guidelines require that sensitivity samples should include individuals in the early phase of infection and after seroconversion (within the first 21 days and after 21 days of symptom onset), as well as samples from asymptomatic or subclinical and mildly symptomatic individuals who may have lower antibody titers.

Compared to this, the sensitivity presented considered mainly the early phase of infection, while the detection period for later time points (31 days after symptom onset) was not fully evaluated. Moreover, the performance evaluation report provided does not describe whether asymptomatic individuals and individuals with mild Covid-19 infection were included. The suitability of the test for very recently vaccinated individuals as also requested by the CS guidance, was not addressed. The manufacturer did not describe from which variant the coated antigens were derived from.

Altogether this information is regarded important, but it is known from current evidence, that anti-SARS-CoV-2 IgM declines rapidly about 30 days after a proven infection and that antibody levels and test sensitivity depend on the severity of Covid-19. It is also known that anti-SARS-CoV-2 IgM may develop differently in vaccinated individuals than in primary infected individuals or may not be present in the case of booster vaccination. This should be more clearly addressed.

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

A PMPF was not available; only a PMPF plan was submitted. Data from PMS may be useful to evaluate the clinical utility of the test in light of more recent data that may be available by this time.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report
The presented approach for the performance evaluation of this test is acceptable and in line with the current MDCG 2021 guidance on SARS-CoV-2, which is expected to be the actual final CS. Most performance parameters have been evaluated sufficiently well. Some requirements of the CS guidance regarding sensitivity, though, have not been fully addressed yet: (i) specification of detection duration after the seroconversion phase, (ii) whether the claimed sensitivity of the test also applies to asymptomatic and mildly infected individuals, who make up the majority of individuals and usually have lower antibody titres, (iii) how the test responds in freshly vaccinated individuals, (iv) and the possible influence of different SARS-CoV-2 variants. The samples required for this may not have been available at the time of the performance evaluation. On the other hand, the intended use is rather general, with a correspondingly broad claim for the diagnostic application of the test, which, however, is so far not fully reflected in the evaluation data presented. Considering the medical progress in the meantime and the importance of SARS-CoV-2, it is considered reasonable to suggest the manufacturer to review the specifications and limitations of the test performance again and update them with more current data.

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.

[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

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

[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.