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	29/10/2021
Notified Body Number	2797
Internal PECP dossier #	IVD-2021-000008
In vitro diagnostic medical device	The device is a qualitative real-time PCR test for the simultaneously detection and differentiation of SARS-CoV-2, Influenza A, and Influenza B in respiratory specimens (Nasopharyngeal swab/nasal swab)

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)*	- SARS-CoV-2 ORF1 a/b non-structural region and nucleocapsid protein gene - Influenza A matrix gene - Influenza B non-structural protein gene
P2	function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc*	Detection and differentiation of Influenza A, Influenza B, and SARS-CoV-2 in respiratory specimens
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.*	Influenza A infection, Influenza B infection, SARS CoV-2 infection
P4	whether it is automated or not	Yes, automated
P5	whether it is qualitative, semi-quantitative or quantitative	Qualitative
P6	type of specimen(s)	Nasopharyngeal swab

	e.g. whole blood, serum, saliva etc	Nasal Swab
P7	where applicable, the testing population *e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range*	Individuals suspected of respiratory viral infection consistent with COVID-19 by their healthcare provider
P8	intended user	Health professionals or trained operators who are proficient in using the automated platform, including in Near Patient Testing environments
Technology (T)		
T1	principle of the assay method or principles of operation of the instrument *e.g. real-time PCR, qualitative PCR, digital PCR, sandwich immunoassay, competitive immunoassay, immunoturbidimetric assay etc.*	Real-time PCR

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group

Date of views	10/01/2022
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-8

3.2 Summary of expert panel views

The proposed assay is an *in vitro* qualitative real-time nucleic acid test (NAT) test for the simultaneously detection and differentiation of SARS-CoV-2, Influenza A, and Influenza B in nasopharyngeal swabs or nasal swabs.

The technology is state of the art and commonly used. The results of the assay are available within 20 minutes. The assay is used to detect and differentiate between SARS-CoV-2, influenza A (both H1N1pdm09 and H3N2), and influenza B viruses (both Yamagata and Victoria).

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.

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

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 assay is intended for the simultaneous and rapid *in vitro* qualitative detection and differentiation of SARS-CoV-2, influenza A, and influenza B virus RNA in healthcare provider-collected nasopharyngeal and nasal swabs as well as in and self-collected nasal swabs (collected in a healthcare setting with instruction by a healthcare provider) from individuals suspected of a viral respiratory infection. 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 detection of SARS-CoV-2, influenza A virus, and influenza B virus nucleic acid 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, ProQuest/Dialog® search (including BIOSIS Previews®, Embase®, and MEDLINE®) and Google Scholar. The data provided are collected until August 2021. No update after this date was further analysed. Comparisons of the assay with other CE-IVD assays on the marker were also identified.
2. Expert views on the analytical performance report[2]
Data on the analytical performance of the assay is documented in DH-05978.01-012B (Assay development summary report) and specifically in Table 2 to 10. According to the manufacturer, the assay shows acceptable performance, demonstrating that this SARS-CoV-2 & Influenza A/B Test is suitable for its intended purpose and detects SARS-CoV-2 targets as well as Influenza A/B targets with sufficient accuracy and precision. The SARS-CoV-2 assay is directed against two targets (RdPd-gene and N-gene), while the influenza A assay is directed against the M-gene, and the influenza B assay is directed against a non-structural protein gene (not further specified). The two-target design of the SARS-CoV-2 assay complies with the dual-target design recommended by the MDCG 2021-21 “Guidance on performance evaluation of SARS-CoV-2 in vitro diagnostic medical devices”.

[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

Mentioned are the information that the assay performance evaluation studies were designed based upon the EUA Interactive Review with the FDA and the internal product requirements. Most Influenza A/B performance data will be leveraging FRTA assay with the successful demonstration of performance equivalency.

The following studies were included in the analytical performance evaluation (results shown):

- SARS-CoV-2 Analytical Sensitivity (LoD): concentration level with observed hit rates greater than or equal to 95% was 0.012 TCID50/mL for SARS-CoV-2. More specifically, the LoD was determined using the WHO International Standard (NIBSC code 20/146) as described in DH-05978.01-153F using Probit Predicted LoD and determined as 67.6 IU/mL (95% confidence interval 44.1-157.3 IU/mL).
- SARS-CoV-2 Reactivity/Inclusivity in silico analysis: The analyses indicated no predicted impact on the SARS-CoV-2 test performance with the dual target design.
- Influenza A/B Analytical Sensitivity Comparison to FRTA: the Probit predicted 95% hit rates for Influenza A were 0.0007 and 0.0009 TCID50/mL for the SARS-CoV-2 & Influenza A/B and the Influenza A/B & RSV tests, respectively. The Probit predicted 95% hit rates for Influenza B were 0.0018 and 0.0026 TCID50/mL for the SARS-CoV-2 & Influenza A/B and the Influenza A/B & RSV tests, respectively. The concentration levels with observed hit rates greater than or equal to 95% were 0.001 TCID50/mL for Influenza A and 0.004 TCID50/mL for Influenza B for both the SARS-CoV-2 & Influenza A/B and the Influenza A/B & RSV tests.
- Influenza A/B Clinical Sample and Strain Performance Comparison to FRTA: all positive clinical samples tested positive by both tests. It must be mentioned that the dynamic range, as expressed in Ct value of these samples, was not provided.
- SARS-CoV-2 Cross-Reactivity – in Silico Analysis: No potential unintended cross-reactivity is expected based on this in silico analysis. In DH05978.01-123F, and analysis has been performed on cross reactivity of the strains involved with other potential targets in respiratory samples at high concentrations (both viral, bacterial, and fungal targets), with no interference.
- SARS-CoV-2 Cross-Reactivity - Wet Test: None of the concentrations tested interfered with the SARS-CoV-2 & Influenza A/B test performance by generating false positive results as described in DH-05978.01-123F.
- SARS-CoV-2 Clinical Evaluation - Correlation of the SARS-CoV-2 test on reference molecular diagnostics systems. In DH-05978.01-229B, the performance between the two systems was described in the Performance Evaluation Report (PER). The conclusion was that the requirements of Annex XIII, Section 1.3, specifically in Annex XIII, Section 1.3.2 of the IVDR have been met, both clinically, scientifically as well as analytically
- Whole system failure rate was determined for the different analytes, following the MDCG 2021-21 “Guidance on performance evaluation of SARS-CoV-2 in vitro diagnostic medical devices” and shown to fulfil the respective requirement (<1% false-negative test results; DH-05978.01-130B).

Microbial interference testing for SARS-CoV-1 was performed using the Urbani strain (BEI Resources, VA, USA) at a concentration of 100.000 PFU/ml. No cross-reactivity was observed. Furthermore, an interference study was performed with endogenous and exogenous substances commonly

encountered in respiratory specimens (see DH-05978.01-109F) with no inhibition of the targets involved.

The performance evaluation of the assay was executed by the manufacturer, with the following testing conditions: 1 culture of heat inactivated SARS-CoV-2 virus, 1 recombinant SARS-CoV-2 virus, ≥ 1 culture of Influenza A, 1 culture of Influenza B viruses, 3 Assay tube lots, 2 PC lots (All were Pilot lots manufactured in Operations), and multiple analyzer systems.

It should also be mentioned that the following influenza A strains were also detected, H5N1, H7N9 and H3N2v.

The following studies were not performed (and rationale provided by manufacturer):

- Measuring range, Linearity and Limit of Quantitation: the SARS-CoV-2 & Influenza A/B Test is a qualitative test and only reports the presence or absence of the test targets.
- Near-Patient Testing: studies including Operating Temperature, Humidity, Altitude/Pressure, Assay Tube seal break, Tilt Testing and Improper tube storage, and Assay workflow were not tested since it has been already established that the system is robust under the variable range of these environmental conditions. These control measurements are system specific and not related to assay chemistry. Studies including Incorrect sample volume, Improper tube storage were not tested since the assay tube configuration, fill volume, reagent formulation and assay chemistry are the same as the Influenza A/B & RSV test previously developed by the manufacturer except for the replacement of RSV oligos with SARS-CoV-2 oligos, therefore the same outcome is expected.

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

Demonstration of the clinical performance of the device has been based on a combination of analytical performance data, a retrospective evaluation of historical clinical data collected prior to IVDR enactment, and scientific peer-reviewed literature. These historical clinical data demonstrate performance, safety and efficacy of the assay and establish robust medical value for the detection and differentiation of SARS-CoV-2, influenza A, and influenza B in the intended use population. Additionally, evidence from supporting peer-reviewed publications, including original and review journal articles and recommended clinical guidelines obtained from a thorough review of the literature further support the clinical performance of the SARS-CoV-2 & Influenza A/B test.

The provided documentation supports the clinical performance of the SARS-CoV-2 & Influenza A/B test and therefore the requirements of Section 1.2.3 of Annex XIII of the IVDR have been met.

The manufacturer states that additional clinical data supporting the product's performance have been generated under the In Vitro Diagnostic Directive (IVDD) from studies executed prior to IVDR enactment (referred to as historical clinical data). These data constitute "Other Sources of Clinical Performance Data," and provide substantial and relevant evidence supporting the performance, safety, and efficacy of the SARS-CoV-2 & Influenza A/B test. A retrospective evaluation of these other sources of clinical performance data, in combination with the clinical performance studies and scientific peer-reviewed literature, have been used to comply with Annex XIII, Section 1.2.3 of the IVDR.

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

No clinical performance studies have been performed for the SARS-CoV- 2 & Influenza A/B test under IVDR. A literature search report including relevant favorable and unfavorable publications has been summarized within the documentation provided.

Eight different studies provide clinical performance evidence:

- An analytical method correlation study using clinical samples, which compares the SARS-CoV-2 & Influenza A/B test to the SARS-CoV-2 test on the reference molecular diagnostics systems.
- Four studies that are a retrospective evaluation of the historical clinical data generated in support of the on-market, CE-approved Influenza A/B & RSV test, previously developed by the same manufacturer. The SARS-CoV-2 & Influenza A/B test was developed based on the Influenza A/B & RSV test, with the SARS-CoV-2 target replacing the RSV target. Therefore, these studies that were executed under IVDD, prior to the enactment of the IVDR, provide evidence in support of the clinical performance, reproducibility, POC use, and cut-off of the SARS-CoV-2 & Influenza A/B test for the influenza A and influenza B targets.
- A performance equivalency study between the SARS-CoV-2 & Influenza A/B test and the Influenza A/B & RSV test.
- A method comparison study between the SARS-CoV-2 & Influenza A/B test and the SARS-CoV-2 test on reference molecular diagnostics systems.
- A reproducibility study.

The following studies were included in the clinical performance evaluation (results shown):

- SARS-CoV-2 Clinical Evaluation - Correlation to the SARS-CoV-2 test on reference molecular diagnostics systems: The results demonstrated 100% positive percent agreement and 100% negative percent agreement between the SARS-CoV-2 test for use on the reference molecular diagnostics systems and the SARS-CoV-2 & Influenza A/B test at hand. The minimum and maximum Cts generated from these positive clinical specimens were 10.8 – 30.3, indicating that the positive samples tested in the study were spanning the test dynamic range. Testing results indicated that low concentrations (~3x LoD) of SARS-CoV-2 can be detected when Influenza A/B was present at a high concentration of 4.7E6 and 1.67E3 fold higher than 3 x LoD, respectively (Table 13). Testing results indicated that low concentrations of Influenza A and Influenza B can be detected in the presence of high concentrations of SARS-CoV-2 that is 1000-fold higher than 3x LoD (Table 13). Naturally occuring SARS-CoV-2 concentrations may exceed the chosen concentration and should be considered for respective investigations in future.
- SARS-CoV-2 Analytical Sensitivity Comparison to the SARS-CoV-2 test on reference molecular diagnostics systems: the SARS-CoV-2 & Influenza A/B test at hand has similar analytical sensitivity as compared with the SARS-CoV-2 test for use on the reference molecular diagnostics systems in detecting SARS-CoV-2 target.
- Media Equivalency and Stability – UTM vs 0.9% Saline: Results suggested similar IC results using regular flocked swabs as compared with mini-tip flocked swabs. For the media equivalence evaluation, simulated matrices were used, which showed both matrices to be equivalent.

The assay cut-off was kept unchanged for RSV in FRTA. After analysing all TPV study data, algorithm and SARS-CoV-2 cut-off updates were implemented in the final script. The SARS-CoV-2 Ct cut-off criteria were updated using observed distribution of sample results and selected to maximize sensitivity and specificity.

Based on the data analysis as shown below, the result calling for SARS-CoV-2 target Ct was changed from 37.3 to 37.5.

Furthermore, the threshold for the FppMax value was updated from 0.0006 to 0.0005 to increase sensitivity without introducing any false positive results.

Data on the sensitivity in relation to the different Variants of Concern (VoC) are limited. However, as shown in the inclusivity study, the SARS-CoV-2 & Influenza A/B test can detect multiple SARS-CoV-2 strains/variants (WHO variants of concern and variants of interest, alpha, beta, gamma, delta, epsilon, Iota, Kappa).

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 perform combined detection and simultaneous differentiation of SARS-CoV-2, influenza A, and influenza B reduces the need for multiple specimen collections in individuals presenting with symptoms that are consistent with both diseases and can detect possible co-infections. Demonstration of the clinical performance of the device has been based on a combination of analytical performance data, a retrospective evaluation of historical clinical data collected prior to IVDR enactment, and scientific peer-reviewed literature. These historical clinical data demonstrate performance, safety and efficacy of the assay and establish robust medical value for the detection and differentiation of SARS-CoV-2, influenza A, and influenza B in the intended use population. 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. Searches were performed in August 2021, in the PubMed database, ProQuest/Dialog® search (including BIOSIS Previews®, Embase®, and MEDLINE®)

and Google Scholar, with appropriate filters applied. The conclusion at that time were a selection of 344 potentially relevant articles before de-duplication. The evidence from supporting peer-reviewed publications, including original and review journal articles, and recommended clinical guidelines obtained from a thorough review of the literature further support the clinical performance of the SARS-CoV-2 & Influenza A/B test, as stated by the manufacturer.

Looking at a more recent literature search (3rd January 2022) in PubMed with the search items "*analyzer name"* & "COVID-19", already identified ten 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 nucleic acid-based assay on an automated multiplex real-time RT-PCR assay intended for the simultaneous rapid *in vitro* qualitative detection and differentiation of SARS-CoV-2, influenza A, and influenza B virus RNA.

The intended purpose of the assay is to detect and differentiate *in vitro* SARS-CoV-2, influenza A virus, and influenza B virus nucleic acid in clinical specimens simultaneously and rapidly.

SARS-CoV-2, influenza A and influenza B viral RNA is generally detectable in respiratory specimens during the acute phase of infection. Positive results are indicative of active infection but do not rule out bacterial infection or co-infection with other pathogens not detected by the test. Clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status. The agent detected may not be the definite cause of disease.

Negative results do not preclude infection from SARS-CoV-2, influenza A, and/or influenza B and should not be used as the sole basis for diagnosis, treatment, or other patient management decisions. Negative results must be combined with clinical observations, patient history, and/or epidemiological information.

The technology is intended for use by health professionals or trained operators who are proficient in using the technology at the point of care (POC) or in a clinical laboratory setting.

A Product Risk Assessment was carried including a Medical Risk Assessment. 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.

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 adequately.

Demonstration of the clinical performance of the device has been based on a combination of analytical performance data, a retrospective evaluation of historical clinical data collected prior to IVDR enactment, and scientific peer-reviewed literature. These historical clinical data demonstrate

performance, safety and efficacy of the assay and establish robust medical value for the detection and differentiation of SARS-CoV-2, influenza A, and influenza B in the intended use population.

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 performance and the clinical value of the assay for the intended purpose. The studies documented widely comply with the MDCG 2021-21 "Guidance on performance evaluation of SARS-CoV-2 in vitro diagnostic medical devices". Common Specifications (or related EU guidance) specific for Influenza detection assays is not yet existing. The technology is state-of-the art. The information provided by the manufacturer shows its principal compliance with the IVDR requirements. It would be recommended to provide an update search of the literature. The ability to detect new variants of concern of SARS-CoV-2 should be continuously checked as part of a post-market performance follow-up and updated information made available, like now with the dominant omicron variant.

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.