Government of Canada / Gouvernement du Canada
MEMORANDUM / NOTE DE SERVICE

TO
Rosslynn Miller-Lee
Executive Director,
Medical Device Evaluation Bureau
MDD

FROM / DE
Maria Carballo, Manager
IVD Device Evaluation Division
MDD

SUBJECT / OBJET
Recommendation for Authorization under Interim Order COVID-19

Manufacturer: ORTHO-CLINICAL DIAGNOSTICS INC.

Device:

- VITROS® Immunodiagnostic Products Anti-SARS-CoV-2 Total Reagent Pack
- VITROS® Immunodiagnostic Products Anti-SARS-CoV-2 Total Calibrator
- VITROS® Immunodiagnostic Products Anti-SARS-CoV-2 Total Controls

***Technology:*** Serology (Total Antibody) ***Setting:*** Laboratory

**Application No.: 314476**

**Background**

On April 22 2020 Health Canada received an application for authorization under the Interim Order of the VITROS® Immunodiagnostic Products Anti-SARS-CoV-2 Total Reagent Pack, and its calibrator and controls, submitted by Ortho Clinical Diagnostics. The device is intended for the serological measurement of Total antibody to SARS-CoV-2 in human serum and plasma (K2 EDTA) samples.

The VITROS® Immunodiagnostic Products Anti-SARS-CoV-2 Total Assay and Total calibrator and controls received a US FDA EUA on April 14, 2020.

The application was reviewed under the Interim Order 32 Respecting the Importation and Sale of Medical Devices for Use in Relation to COVID-19 pursuant to 33 subsection 30.1(1) of the Food and Drugs Act. This Interim Order will allow the Department to issue expedited authorization for sale or import of medical devices to deal with the current significant risk of COVID-19 to the health and safety of Canadians.

The information submitted was evaluated based on the following:

- Health Canada "Draft Guidance Document Applications for Medical Devices" under the *Interim Order* ***Respecting the Importation and Sale of Medical Devices*** *for Use in Relation to COVID-19* (March 2020)
- Health Canada Guidance: Requirements for Serological Antibody testing submitted under COVID-19 Interim Order

  https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/covid19-requirements-serological-antibody-tests.html

***Intended Use***

**The VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Total Reagent Pack** test when used in combination with the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Total Calibrator is for the qualitative measurement of total antibody (including IgG, IgA and IgM) to SARS-CoV-2 in human serum and plasma (K2 EDTA) samples from patients suspected of COVID-19 by a healthcare provider, using VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems. The VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Total test is intended for use as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection.

Results are for the detection of total SARS-CoV-2 antibodies. Reactive results could occur after infection and can be indicative of acute or recent infection.

Non-reactive results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. Results must be combined with clinical observations, patient history, and epidemiological information. The sensitivity of the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Total Reagent Pack test early after infection is unknown. False reactive results may occur due to cross-reactivity from pre-existing antibodies or other possible causes.

At this time, it is unknown for how long antibodies to SARS-CoV-2 virus may persist following infection.
[Pub. No. GEM1293_CA_EN Version 1.0 2020-05-22 – Revised June 3 2020]

**VITROS Immunodiagnostic Products Anti−SARS-CoV-2 Total Controls**

For use in monitoring the performance of the VITROS Immunodiagnostic and Integrated Systems when used for the determination of antibodies to SARS-CoV-2. Control
[Package insert Version 1.0, 2020-04-08]

**Discussion:** The information provided meets the minimum requirements for issue of Authorization under Interim Order 32.

The assay runs on well established class IV licensed platforms, the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems.

The manufacturer holds a valid MDSAP Certificate.

Overall, data from Analytical and Clinical studies meet the requirements of the HC Guidance on Serology antibody tests with the exceptions noted in the conditions.

Analytical studies showed the sample matrices recommended for use with the assay, serum and plasma $K_2$EDTA, to be equivalent. Interference studies demonstrated that bilirubin (conjugated and conjugated), biotin, hemoglobin and intralipid, tested at concentrations recommended by CLSI EP-07-A2, did not interfere with the assay's performance. The remaining recommended exogenous and endogenous interferents to be tested are the subject of a condition. No cross-reactivity was observed when testing samples from medical conditions unrelated to SARS-CoV-2. As not all the pathogens identified in the HC Guidance were tested, these studies will be subject to a condition. Data from the clinical specificity study on pre-pandemic samples indirectly show no cross-reactivity with common coronaviruses. Evidence in the literature demonstrates there is seroprevalence of other coronaviruses in healthy populations with a reported proportion of seropositive adults for each coronavirus as follows: 229E, 91.3%; HKU1, 59.2% or higher; NL63, 91.8%; and OC43, 90.8%. These data provide an indication that these viruses have an already established presence in the study population. In addition is worth noting that the Ortho Total antibody assay uses the spike S1 protein (antigen) of the SARS-CoV-2 virus which has been reported to be superior to the nucleocapsid protein in terms of Specificity & Cross-Reactivity.

The current claimed stability of the reagent pack of 26 weeks is acceptable based on the experience of the manufacturer with existing Class IV licensed tests. The protocol provided to evaluate shelf life, and onboard stability is acceptable. Completion of stability studies is the subject of the conditions imposed on the Authorization.

Clinical sensitivity studies met the Health Canada requirements of a minimum of 50 positive samples. Samples from 86 individual patients confirmed to be SARS CoV-2 positive by PCR (Abbott RealTi*m*e SARS-CoV-2 PCR HC Authorized under IO) were collected. For 69 of the 86 samples, the date of sample collection and date of onset of symptoms were provided. The sensitivity was 100% at both $\leq 8$ days and $> 8$ days (after symptom onset. The 95% CI lower interval at $\leq 8$ days is 79.4 demonstrating, as expected lower sensitivity closer to symptom onset.

| Days Since Symptoms Reported* | Number Reactive | Number Non-reactive | Total Number Tested | Sensitivity (95% CI) |
|---|---|---|---|---|
| ≤ 8 | 16 | 4** | 20 | 100.0% (79.4 to 100.0%) |
| > 8 | 49 | 0 | 49 | 100.0% (92.7 to 100.0%) |

* An additional 17 samples were tested but information about date of symptom onset was not available. Of those 17 samples, 15 were Reactive and 2 were Non-Reactive.
** These samples were negative for neutralizing antibody and removed from the Sensitivity calculation.

Clinical specificity was established on 400 random donor samples from the US population, 380 of these samples were collected in the United States prior to February 2020, before widespread outbreak of SARS-CoV-2 in the country and therefore presumed to be SARS-CoV-2 naive. The other 20 samples were collected in the United States in March 2020. As requested, an additional data set was provided to complete the HC required 500 samples: 120 negative serum samples, sourced from donors in June 2019 and an additional 100 pre-pandemic tested by the British Columbia Center for Disease

Control (BCCDC) with the VITROS Anti-SARS-CoV-2 TOTAL Assay. Thus a total of 600 samples, confirmed to be pre-pandemic sourced, were tested showing a 100% specificity.

The HC requirement for testing 200 PCR negative samples from symptomatic patients for specificity testing was not met. However, it was agreed internally that this requirement will not be enforced at this time as Health Canada is reconsidering the wording, intent, and best approach to obtain this information. This is consistent with decisions taken for the Authorized LIAISON SARS-COV-2 S1/S2 IGG test kit (application 314838) and the Architect SARS CoV-2 IgG assay (Application 314941).

Changes to the labelling were implemented as requested, resulting in a Canadian specific package insert that meets the requirements of the Regulations and the HC Serological antibody tests guidance.

In the context of the COVID-19 pandemic, the evidence provided by the manufacturer provide reasonable assurance that the VITROS® Immunodiagnostic Products Anti-SARS-CoV-2 Total Reagent Pack, Calibrators and Controls, will perform as claimed for their intended use under the current COVID-19 national health emergency.

**RECOMMENDATION:**

Issue an Interim Order Authorization for the VITROS® Immunodiagnostic Products Anti-SARS-CoV-2 Total Reagent Pack, Calibrators and Controls, with the following conditions:

1. Stability studies, please provide:
    a. when available, the 26-week stability data for the reagent pack, controls and calibrators and the 52 week data by Nov. 2021.
    b. when available, the results of the shelf life, on-board, off-board and transport stability studies for the reagent pack, calibrators and controls.
    c. results of the specimen stability study by Dec. 31, 2020.

2. Provide an evaluation of repeatability and reproducibility.

3. Provide evaluation of interference with protein (e.g. albumin), rheumatoid factor, hemoglobin (at 2g/L), hematocrit, total IgM, total IgG and medications most often prescribed in the patient population.

4. Provide by July 10, 2020, a plan to assess cross-reactivity for the complete list of mandatory organisms per the Health Canada guidance with 5 pre-pandemic samples positive for IgM, IgG and IgA antibodies. When available, provide a summary of the results obtained from cross-reactivity studies.

5. Submit by July 10, 2020, a plan that will assess the performance of the device when used in the intended sites. The plan should include:
    a) Identification of a minimum of two Canadian sites where the performance of the test will be monitored;
    b) Methodology to collect supplementary clinical performance data to support or

revise the performance claims; and
c) Submission of a report with a summary of the clinical performance data to Health Canada every three months after implementation of the plan. Collection of the clinical data should begin at Canadian sites within two weeks after Health Canada reviews the plan to assess clinical performance.

I concur / Je suis d'accord

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| | 2020-06-04 | | |
| **Maria Carballo**<br>Manager, In Vitro Diagnostic Section / chef, Matériels diagnostiques in vitro<br>Device Evaluation Division / Division de l'Évaluation des Matériels | Date | **Rosslyn Miller-Lee**<br>Executive Director/ Directrice Executive<br>Medical Devices Evaluation Bureau/ Bureau de l'évaluation des instruments médicaux | Date |