Ortho-Clinical Diagnostics, Inc.
Marlene Hanna
Director, Regulatory Affairs
100 Indigo Creek Drive
Rochester, New York 14626

May 5, 2023

Re: DEN210038
Trade/Device Name: VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Reagent Pack, VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Calibrator
Regulation Number: 21 CFR 866.3983
Regulation Name: SARS-CoV-2 serology test
Regulatory Class: Class II
Product Code: QVP
Dated: September 17, 2021
Received: September 20, 2021

Dear Marlene Hanna:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Reagent Pack, VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Calibrator, a prescription device with the following indications for use:

Rx ONLY

For in vitro diagnostic and laboratory professional use.

VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Reagent Pack

The VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Reagent Pack when used in combination with the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Calibrator is a chemiluminescent immunoassay intended for the qualitative detection of IgG antibodies to SARS-CoV-2 in human serum and plasma (K2-EDTA and K3-EDTA) samples collected on or after 15 days post-symptom onset using the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems. The VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG 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.

VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Calibrator

> For use in the calibration of the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems for the in vitro qualitative detection of IgG antibodies to SARS-CoV-2 in human serum and plasma.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Reagent Pack, VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Calibrator, and substantially equivalent devices of this generic type, into Class II under the generic name SARS-CoV-2 serology test.

FDA identifies this generic type of device as:

> **SARS-CoV-2 serology test**. A SARS-CoV-2 serology test is a prescription in vitro diagnostic device for the detection of specific binding antibodies to SARS-CoV-2 in clinical specimens. The detection of SARS-CoV-2 antibodies is intended to aid in identifying individuals with an adaptive immune response to SARS-CoV-2. The test is not intended for the diagnosis of acute SARS-CoV-2 infection, nor screening blood, plasma, cells, or tissue donors.

Section 513(f)(2) of the Federal Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register announcing the classification.

On September 20, 2021, FDA received your De Novo requesting classification of the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Reagent Pack, VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Calibrator. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Reagent Pack, VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Calibrator into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the De Novo request, FDA has determined that, for the previously stated indications for use, the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Reagent Pack, VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Calibrator can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Risks to Health	Mitigation Measures
Risk of false test results	Certain labeling information including limitations, device descriptions, explanations of procedures and performance information identified in special controls (1), (3), and (5). Use of certain specimen collection devices identified in special control (2). Certain design verification and validation including documentation of device descriptions, certain analytical studies and clinical studies, and risk analysis strategies identified in special control (4). Testing of characterized samples and labeling information identified in special control (6).
Failure to correctly interpret the test results	Certain labeling information including limitations, device descriptions, explanations of procedures and performance information identified in special controls (1), (3), and (5). Use of certain specimen collection devices identified in special control (2). Certain design verification and validation including documentation of device descriptions, certain analytical studies and clinical studies, and risk analysis strategies identified in special control (4). Testing of characterized samples and labeling information identified in special control (6).
Failure to correctly operate the device	Certain labeling information including limitations, device descriptions, explanations of procedures and performance information identified in special controls (1), (3), and (5). Use of certain specimen collection devices identified in special control (2).

In combination with the general controls of the FD&C Act, the SARS-CoV-2 serology test is subject to the following special controls:

(1) The intended use in the labeling required under 21 CFR 809.10 must include a description of the following: Analytes the device detects, the specimen types tested, the results provided to the end user, the clinical indications for which the test is to be used, the specific intended population(s), the intended use locations including testing location(s) where the device is to be used (if applicable), and other conditions of use, as appropriate.

(2) If sample collection devices are used, any sample collection device used must be FDA-cleared, -approved, or -classified as 510(k) exempt (standalone or as part of a test system) for the collection of specimen types claimed by this device; alternatively, the sample collection device must be cleared in

a premarket submission as a part of this device.

(3) The labeling required under 21 CFR 809.10(b) must include:

(i) A detailed device description, including reagents, instruments, ancillary materials, all control elements, and a detailed explanation of the methodology, including all pre-analytical methods for processing of specimens;
(ii) Detailed descriptions of the performance characteristics of the device for each specimen type claimed in the intended use based on analytical studies including the following, as applicable: Assay cutoff or limit of detection expressed in international standard units, inclusivity, cross-reactivity, interfering substances, competitive inhibition, carryover/cross contamination, matrix equivalency, hook effect, specimen stability, precision, reproducibility, and clinical studies, including the time period in which the clinical performance was established and the variant(s) prevalent in the US at the time of performance validation;
(iii) Detailed descriptions of the test procedure(s), the interpretation of test results for clinical specimens, and acceptance criteria for any quality control testing;
(iv) When applicable, performance results of the analytical study testing of a standardized reference material that FDA has determined is appropriate;
(v) Limiting statements that indicate:
  (A) A negative test result does not preclude the possibility of infection;
  (B) A negative result can occur if the quantity of the anti-SARS-CoV-2 antibodies present in the specimen is below the detection limits of the assay, or the antibodies that are detected are not present during the stage of disease in which a sample is collected;
  (C) There is a risk of erroneous results (i.e., negative results) due to the presence of novel emerging viral variants circulating in the intended use population;
  (D) The performance characteristics for that analyte were established when [insert predominant strain, subtype, or variant] was prevalent and that due to the propensity of the virus to mutate, new strains emerge over time which may affect the performance of this device and have serious public health implications;
  (E) The test results should be interpreted in conjunction with other clinical and laboratory data available to the healthcare provider (as applicable);
  (F) That positive and negative predictive values are highly dependent on prevalence;
  (G) Accurate results are dependent on adequate specimen collection, transport, storage, and processing (as applicable). Failure to observe proper procedures in any one of these steps can lead to incorrect results;
  (H) The test is not intended for donor screening; and
  (I) The test is not intended to diagnose acute SARS-CoV-2 infection. An assay that directly detects the virus should be used to evaluate individuals for acute COVID-19, particularly those who have been in contact with the virus.
(vi) For devices intended for the quantitative detection of SARS-CoV-2 antibodies, labeling must include a prominent statement that includes the following: the test calibrators' traceability to a standardized reference material that FDA has determined is appropriate and the limit of blank, limit of detection, limit of quantitation, with the defined analytical measuring interval.

(4) Design verification and validation must include:

(i) Detailed documentation of performance from a multisite clinical study with an appropriate number of clinical samples (be appropriately statistically powered) from individuals with recent or prior SARS CoV-2 infection in which the results are compared to results obtained from a comparator that FDA has determined to be appropriate. This study must be conducted in the appropriate laboratory setting to demonstrate clinical performance. For any SARS-CoV-2 serology test intended for use in near-patient settings, a separate clinical study must be conducted in near-patient settings. Documentation from these studies must include study reports with study description, testing results, and all statistical analyses, including an appropriate justification describing how the sample set is representative of the intended use population. These studies must compare the device performance to results obtained from a comparator that FDA has determined to be appropriate. These clinical studies must include testing of unique prospective samples from subjects that are representative of the intended use populations and may, when determined to be acceptable by FDA, include additional characterized clinical samples; or, as an alternative, when determined to be acceptable by FDA, an equivalent sample set;

(ii) For any SARS-CoV-2 antibody test intended for use in near-patient settings, detailed documentation that demonstrates the effectiveness of risk control measures and device robustness, including flex studies, and performance with weakly-reactive samples when used by the intended operators;

(iii) Risk analysis and documentation demonstrating how risk control measures are implemented to address device system hazards, such as Failure Modes Effects Analysis and/or Hazard Analysis. This documentation must include a detailed description of a protocol (including all procedures and methods) for the continuous monitoring, identification, and handling of genetic mutations and/or novel respiratory pathogen isolates or strains (*e.g.,* regular review of published literature and periodic *in silico* analysis of target amino acid sequence(s) to detect possible mismatches) that may affect detection of antibody. All results of this protocol, including any findings, must be documented and must include any additional data analysis that is requested by FDA in response to any performance concerns identified under this section or identified by FDA during routine evaluation. Additionally, if requested by FDA, these evaluations must be submitted to FDA within 48 hours of the request for FDA review and any results that are reasonably interpreted to support the conclusion that novel respiratory pathogen strains or isolates impact the stated expected performance of the device must be sent to FDA immediately to the email provided in FDA's request;

(iv) Documentation of the specific amino acid sequence of the SARS-CoV-2 target protein(s) that the device utilizes to detect specific antibodies to SARS-CoV-2;

(v) A detailed device description, including device components, ancillary reagents required but not provided, and a detailed explanation of the methodology, including protein sequence target(s) for each analyte, design of target detection reagents, internal and external controls, and computational path from collected raw data to reported result (e.g., how collected raw signals are converted into a reported signal and result), as applicable to the detection method and device design;

(vi) For devices with associated software or instrumentation, documentation must include a detailed description of device software, including software applications and hardware-based devices that incorporate software. The detailed description must include documentation of verification, validation, and hazard analysis and risk assessment activities, including an assessment of the impact of threats and vulnerabilities on device functionality and end users/patients as part of cybersecurity review;

(vii) For devices intended for the detection of SARS-CoV-2 antibodies for which a standardized reference material (that FDA has determined is appropriate) is available, the performance results of an analytical study testing this standardized reference material. Detailed documentation of that study and its results must be provided, including the study protocol, study report, testing results, and all statistical analyses;

(viii) Detailed documentation of analytical studies conducted as appropriate to the technology, specimen types tested, and intended use of the device, including precision, endogenous interferences, cross reactivity, carryover, matrix equivalency, class specificity, hook effect, and sample and reagent stability. Samples selected for use in analytical studies or used to prepare contrived samples for use in analytical studies must be from subjects with clinically relevant circulating antibodies to SARS-CoV-2 in the United States. Cross-reactivity studies must include samples from SARS-CoV-2 antibody negative subjects with antibodies to viruses, high prevalence disease agents, and normal or pathogenic flora. Endogenous interference studies must include SARS-CoV-2 antibody negative and low positive samples with endogenous interference substances, including antibodies present in autoimmune diseases that are reasonably likely to be encountered in clinical specimens under actual use conditions. In addition, for devices intended for the quantitative detection of SARS-CoV-2 antibodies, the information provided must also include the metrological calibration traceability hierarchy to a standardized reference material that FDA has determined is appropriate. As appropriate to the technology and specimen types tested, the information provided to support quantitative tests must also include studies to support the analytical measuring interval, including a limit of blank study, a limit of detection study, an upper and lower limits of quantitation study, a precision study, and a linearity study using clinical samples, and, using a standardized reference material that FDA has determined is appropriate, an accuracy study;

(ix) Detailed documentation of data and protocols, including acceptance criteria, from a real-time reagent stability study must include testing of samples with adequately challenging analyte concentrations and must include shelf-life stability and shipping stability, and, as applicable, in-use/open-kit stability and freeze-thaw stability. The shelf-life stability assessment must include a minimum of three lots;

(x) Detailed documentation of a multisite reproducibility study with testing conducted at a minimum of three sites;

(xi) Final release criteria to be used for manufactured test lots with appropriate evidence that lots released at the extremes of the specifications will meet the claimed analytical and clinical performance characteristics as well as the stability claims; and

(xii) Lot-to-lot precision studies, as appropriate.

(5) For any SARS-CoV-2 antibody test intended for use in near-patient settings, labeling must also include a brief reference sheet (Quick Reference Instructions) for the intended user(s) that includes, at a minimum, the name and intended use of the test, easy to follow step-by-step instructions of all control and sample testing procedures for the claimed sample types, including graphic illustrations targeted towards lay users (as applicable), the result(s) interpretation guidance, warnings and limitation statements, toxicology information and safety considerations for any hazardous materials, information for troubleshooting (e.g., Frequently Asked Questions), and technical assistance with the device (e.g., Help-line contact information).

(6) If one of the actions listed in section 564(b)(1)(A)–(D) of the Federal Food, Drug, and Cosmetic Act

occurs with respect to one or more of the analytes claimed in the intended use, or if the Secretary of Health and Human Services (HHS) determines, under section 319(a) of the Public Health Service Act, that a disease or disorder presents a public health emergency, or that a public health emergency otherwise exists, with respect to one or more of the analytes claimed in the intended use:

(i) Within 30 days from the date that FDA notifies manufacturers that characterized samples are available for test evaluation, the manufacturer must have testing performed on the device with those samples in accordance with a standardized protocol considered and determined by FDA to be acceptable and appropriate; and

(ii) Within 60 days from the date that FDA notifies manufacturers that characterized samples are available for test evaluation and continuing until 3 years from that date, the results of the emergency analytical reactivity testing, including the detailed information for the samples tested as described in the certificate of authentication, must be included as part of the device's labeling in a tabular format.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the SARS-CoV-2 serology test they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD&C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD&C Act; 21 CFR 1000-1050).

A notice announcing this classification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the De Novo request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Maria Esteve-Gasent at Maria.Esteve-Gasent@fda.hhs.gov.

Sincerely,

Uwe Scherf -S

Uwe Scherf, M.Sc., Ph.D.
Director
Division of Microbiology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health