June 15, 2022

Ortho Clinical Diagnostics
Declan Hynes
Senior Regulatory Affairs Manager
Felindre Meadows
Pencoed, Bridgend CF35 5PZ
United Kingdom

Re: K213626
Trade/Device Name: VITROS Immunodiagnostic Products AFP Reagent Pack
Regulation Number: 21 CFR 866.6010
Regulation Name: Tumor-Associated Antigen Immunological Test System
Regulatory Class: Class II
Product Code: LOJ
Received: November 17, 2021

Dear Declan Hynes:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

801 and Part 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 Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, 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).

Sincerely,

Ying Mao, Ph.D.
Chief
Division of Immunology and Hematology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K213626

Device Name

VITROS Immunodiagnostic Products AFP Reagent Pack

Indications for Use *(Describe)*

For the quantitative measurement of alpha-fetoprotein (AFP) concentrations in human serum using the VITRO 5600 Integrated system to aid in the management of patients with non-seminomatous testicular cancer.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K213626

1. **Submitter name, address, contact**

Ortho-Clinical Diagnostics, Inc.
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Rochester, NY 14626
P: (+44) 01656 778032; F: (585) 453-3113
Contact Person: Declan Hynes

2. **Preparation Date** April 29th, 2022

3. **Device Name**: VITROS® Immunodiagnostic Products AFP Reagent Pack

4. **Predicate Device:** VITROS Immunodiagnostic Products AFP Reagent Pack K983031, cleared 18 December 1998

5. **Proprietary and Established Name:** VITROS® Immunodiagnostic Products AFP Reagent Pack

6. **Regulatory Information:**

Product Code	Class	Regulation Section	Panel
LOJ	II	21 CFR 866.6010 Tumor-associated antigen immunological test system.	Immunology (82)

7. Intended Use:

1. Intended use:

For the quantitative measurement of alpha-fetoprotein (AFP) concentrations in human serum using the VITROS 5600 Integrated system to aid in the management of patients with non-seminomatous testicular cancer.

2. Special conditions for use statement:

Rx Only, IVD only

3. Special instrument requirements:

- VITROS 5600 System

I. Device Description:

The VITROS Immunodiagnostic Products AFP Reagent Pack is performed using the VITROS Immunodiagnostic Products AFP Reagent Pack and the VITROS AFP Calibrators on the VITROS 5600 System.

VITROS Immunodiagnostic Products AFP Reagent Pack contains:

1 reagent pack containing:

- 100 coated wells (antibody, sheep anti-AFP, binds ≥25 IU AFP/well)
  - 20.6 mL conjugate reagent (HRP-mouse monoclonal anti-AFP, binds ≥156 IU AFP/ mL) in buffer with bovine serum and antimicrobial agent.
  - 15.8 mL assay reagent (buffer containing bovine serum albumin and antimicrobial agent)

VITROS Immunodiagnostic Products AFP Calibrator contains:

- 1 set of VITROS AFP Calibrators 1, 2 and 3 (human cord serum/plasma derived AFP in human plasma with antimicrobial agent, 2 mL); nominal values 2; 22 and 220 IU/mL (1st International Reference Preparation 72/225) (2.42; 26.6 and 266 ng/mL)
- Lot calibration card
- Protocol card
- 24 calibrator bar code labels (8 for each calibrator)

8. Substantial Equivalence Information:

Predicate device name:

VITROS Immunodiagnostic Products AFP Reagent Pack K983031,

cleared 18 December 1998

8.1 Comparison with predicate: Similarities:

Device Characteristic	Predicate Device VITROS Immunodiagnostic Products AFP Reagent Pack K983031, cleared 18 December 1998	Modified Device VITROS Immunodiagnostic Products AFP
Intended Use	For the quantitative measurement of alpha-fetoprotein (AFP) concentrations in human serum using the VITROS ECi/ECiQ and VITROS 3600 Immunodiagnostic Systems and the VITROS 5600/XT7600 Integrated Systems to aid in the management of patients with non-seminomatous testicular cancer.	For the quantitative measurement of alpha-fetoprotein (AFP) concentrations in human serum using the VITROS 5600 Integrated System to aid in the management of patients with non-seminomatous testicular cancer
Antibody	Monoclonal anti-AFP and Sheep anti-AFP	Same
Sample Type	Serum	Same
Traceability	Calibrated against First International Reference Preparation 72/225.	Same
Measuring Range	0.800–500 IU/mL	Same
Detection Limit	LOB: 0.229 IU/mL LOD: 0.476 IU/mL	LOB: Same LOD: Same IU/mL LOQ: 0.800 IU/mL

Differences:

Basic Principle	Sandwich immunoassay	Sandwich immunoassay. In the modified AFP Reagent Pack the sheep anti-AFP antibody has been removed from the Biotin Reagent and coated directly onto the well. The modification to allow the biotinylated antibody capture conjugate to be pre- bound to the well, eliminates the risk of biotin interference.
Conversion Factor between Units	X 1.04 IU/ml to ng/mL	X 1.21 IU/mL to ng/mL. Different, the adoption of the 1.21 conversion factor will align the VITROS AFP Reagent Pack to other vendors using the same conversion factor.

8.2. Standard/Guidance Document Referenced (if applicable):

CLSI. Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline. CLSI guideline EP25-A. Wayne, PA: Clinical and Laboratory Standards Institute, 2009.

CLSI. Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition. CLSI document EP28-A3c. Wayne, PA: Clinical and Laboratory Standards Institute; 2010.

CLSI. Evaluation of Precision Performance of Quantitative Measurement Methods; Third Edition. CLSI guideline EP05-A3. Wayne, PA: Clinical and Laboratory Standards Institute, 2014.

CLSI. Evaluation of Linearity of Quantitative Measurement Procedures. 2nd ed. CLSI guideline EP06. Clinical and Laboratory Standards Institute, 2020.

CLSI. Interference Testing in Clinical Chemistry - Third Edition. CLSI guideline EP07-A3. Wayne, PA: Clinical and Laboratory Standards Institute, Clinical and Laboratory Standards Institute; 2018

CLSI. Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Second Edition. CLSI guideline EP 17-A2. Wayne, PA: Clinical and Laboratory Standards Institute, 2012.

CLSI. Measurement Procedure Comparison and Bias Estimation Using Patient Samples. 3rd ed. CLSI guideline EP09c. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

CLSI. Supplemental Tables for Interference Testing in Clinical Chemistry. 1st ed. CLSI supplement EP37. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

8.3. Test Principles:

An immunometric immunoassay technique is used. AFP present in the sample reacts with a biotinylated antibody (sheep anti-AFP) bound to streptavidin on a microwell. Unbound sample is removed by washing. In a second incubation a horseradish peroxidase (HRP)-labeled antibody conjugate (mouse monoclonal anti-AFP) binds to the immobilized AFP. Unbound materials are removed by washing.

The bound HRP conjugate is measured by a luminescent reaction. A reagent containing luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent, is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent (a substituted acetanilide) increases the level of light produced and prolongs its emission. The light signals are read by the system. The amount of HRP conjugate bound is directly proportional to the concentration of AFP present.

9. Performance Characteristics (if/when applicable):

9.1. Analytical performance:

a. Precision/Reproducibility:

Precision was evaluated with patient pools on the systems in the table below following the CLSI document EP05.

The data presented are a representation of test performance and are provided as a guideline.

System	Units = IU/mL					No. of Obs.	No. of Days
	Mean AFP Conc.	Repeatability*		Within Lab**			
		SD	%CV	SD	%CV		
5600	2.92	0.055	1.9%	0.067	2.3%	80	20
	11.9	0.20	1.6%	0.33	2.8%	80	20
	77.0	1.51	2.0%	2.12	2.8%	80	20
	236	7.5	3.2%	9.7	4.1%	80	20
	395	9.6	2.4%	17.9	4.5%	80	20

*Repeatability (formerly called within-run precision) was determined using two replicates per run.

**Within Lab precision was determined using a single reagent lot and a single calibration.

b. Linearity/assay measuring range:

The linearity was established in accordance with the CLSI protocol EP06.

Linearity/Measuring Range

VITROS System	Measuring (Reportable) Range
5600	0.800–500 IU/mL

d. Dilution Recovery

Serum samples with concentrations greater than the measuring range may be diluted up to 4000-fold (1 part sample with 3999 parts diluent) with the VITROS High Sample Diluent A. Dilutions of up to 1:400 (1 part sample with 399 parts diluent) may be performed automatically on the VITROS 5600 Integrated System, using the VITROS High Sample Diluent A Reagent Pack.

e. Traceability:

Calibration of the VITROS AFP test is traceable to in-house reference calibrators which have been calibrated against the First International Reference Preparation 72/225.

f. Detection Limits:
The Limit of Detection (LoD) for the VITROS AFP test is 0.476 IU/mL (0.576 ng/mL), determined consistent with CLSI document EP17. The Limit of Quantitation (LoQ) for the VITROS AFP test was determined to be 0.800 IU/mL (0.968 ng/mL) at 20% CV. The Limit of Blank (LOB) is 0.229 IU/mL.

g. Analytical Specificity:

Known Interferences
The VITROS AFP test was screened for interfering substances at AFP concentrations of approximately 4.80 IU/mL (5.81 ng/mL) and 19.2 IU/mL (23.2 ng/mL) following CLSI EP07 and EP37. Of the compounds tested, none were found to cause a bias of >10%. Refer to "Specificity" for a list of compounds that did not show interference.

Other Limitations

- The results from this test should be used and interpreted only in the context of the overall clinical picture.
- Heterophile, as well as human anti-animal antibodies (most common being human anti-mouse antibodies or HAMA) in serum or plasma of certain individuals are known to cause interference with immunoassays. The anti-animal antibodies may be present in blood samples from individuals regularly exposed to animals or who have received preparations of mouse monoclonal antibodies for diagnosis or therapy. Results inconsistent with clinical observations indicate the need for additional testing.
- For changes in tumor marker concentrations during therapy:
    - Progressive disease is defined by an increase of at least 25%. Sampling should be repeated within two to four weeks for additional evidence.
    - Partial remission is defined as a decrease of at least 50% in the tumor marker concentrations.
- Different test methods cannot be used interchangeably. A change to the test used during serial monitoring of a patient should be accompanied by additional sequential testing to confirm baseline concentrations. The results reported to the physician must include the identity of the AFP test used.
- Certain drugs and clinical conditions are known to alter AFP concentrations in vivo. For additional information, refer to one of the published summaries.

Substances that do not Interfere

The substances listed in the table below were tested with the VITROS AFP test following CLSI EP07and EP37 and found not to cause bias > 10% at AFP concentrations of approximately 4.80 IU/mL (5.81 ng/mL) and 19.2 IU/mL (23.2 ng/mL) at the test concentrations shown.

Substance	**Concentration**	
5-Fluorouracil	17 mg/dL	1.31 mmol/L
Acetaminophen	20 mg/dL	1.32 mmol/L
N-Acetylcysteine	15 mg/dL	0.919 mmol/L
Acetylsalicylic acid	50 mg/dL	2.78 mmol/L
Actinomycin D	50 mg/dL	0.40 mmol/L
Alpha-tocopherol	6.45 mg/dL	0.150 mmol/L
Amoxicillin	5.4 mg/dL	0.148 mmol/L
Ascorbic acid	300 mg/dL	17 mmol/L
Bilirubin, conjugated	40 mg/dL	0.475 mmol/L
Bilirubin, unconjugated	40 mg/dL	0.684 mmol/L
Biotin	0.351 mg/dL	3510 ng/mL
Bleomycin sulfate	300 mg/dL	N/A
Cefoxitin sodium	695 mg/dL	15.5 mmol/L
Cisplatin	100 mg/dL	3.33 mmol/L
Cholesterol, total	400 mg/dL	10.3 mmol/L
Codeine	0.141 mg/dL	4.72 µmol/L
Cholecalciferol	19.2 µg/dL	0.499 µmol/L
Cotinine	0.24 mg/dL	13.6 µmol/L
Cyclophosphamide monohydrate	25 mg/dL	0.96 mmol/L
Dextran 40	2400 mg/dL	0.600 mmol/L
Doxorubicin hydrochloride	1 mg/dL	17.2 µmol/L
Enoxaparin	360 U/dL	N/A
Ethanol	600 mg/dL	130 mmol/L
Etoposide	25 mg/dL	0.43 mmol/L
Furosemide	1.59 mg/dL	48.0 µmol/L
HAMA (Human Anti-Mouse	800 µg/L	0.053 µmol/L

Substance	**Concentration**	
Antibodies)		
Hemoglobin	500 mg/dL	77.6 µmol/L
Hydralazine hydrochloride	1.44 mg/dL	73.2 µmol/L
Hydrocodone (+) - bitartrate	0.0072 mg/dL	0.241 µmol/L
Ibuprofen	40 mg/dL	1.94 mmol/L
Intralipid	2000 mg/dL	19.2 mmol/L
Levothyroxine	0.0429 mg/dL	0.552 µmol/L
Loratadine	0.0087 mg/dL	0.227 µmol/L
Methotrexate	450 mg/dL	9.90 mmol/L
Mitomycin C	0.72 mg/dL	21.5 µmol/L
Morphine sulfate salt pentahydrate	0.78 mg/dL	10.3 µmol/L
Naproxen	36 mg/dL	1.56 mmol/L
Omeprazole	0.84 mg/dL	24.3 µmol/L
Phenytoin	6 mg/dL	0.238 mmol/L
Prednisone	0.01 mg/dL	0.279 µmol/L
Rheumatoid factor	900 IU/mL	N/A
Sorafenib	3 mg/dL	64.5 µmol/L
Theophylline	6 mg/dL	0.333 mmol/L
Total protein	15 g/dL	17.1 nmol/L
Triglycerides, total	1500 mg/dL	16.9 mmol/L
Vancomycin hydrochloride	12.3 mg/dL	82.8 µmol/L
Vinblastine sulfate	100 mg/dL	1.23 mmol/L
Vincristine sulfate	70 mg/dL	0.85 mmol/L

Cross-Reactivity

The cross-reactivity of the VITROS AFP test was evaluated by adding the following substances to a sample containing no AFP.

Test Substance	Concentration	% Cross-reactivity
Human α−1− acid glycoprotein	200 mg/dL	ND*
Human α−1− antitrypsin	500 mg/dL	ND*
Human ceruloplasmin	250 mg/dL	ND*
Human chorionic gonadotrophin	1,000,000 mIU/mL	ND*
Human IgG	6.00 g/dL	ND*
Human placental lactogen	2000 µg/dL	ND*
Human serum albumin	6000 mg/dL	ND*
Human transferrin	2500 mg/dL	ND*
Prolactin	50,000 mIU/L	ND*

*Not Detectable. Concentration was below the measuring interval of the test, 0.800 to 500 IU/mL (0.968 – 605 ng/mL)

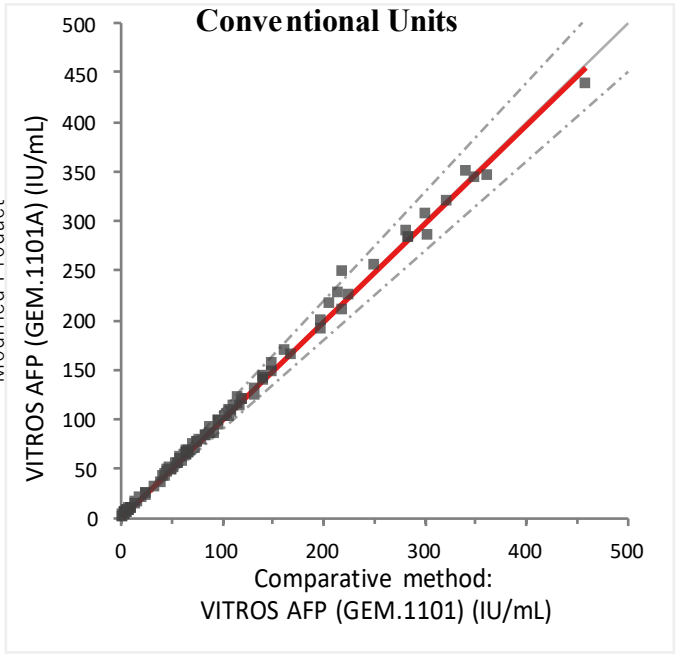
h. Assay cut-off:

Not applicable.

i. Comparison studies:

a. Method comparison with predicate device:

Accuracy was evaluated consistent with CLSI document EP09. The plot and table show the results of a method comparison study using patient (serum) samples analyzed on the VITROS 5600 Integrated System using the candidate VITROS Immunodiagnostic Products AFP Reagent Pack compared with those analyzed using the cleared predicate VITROS Immunodiagnostic Products AFP Reagent Pack. The relationship between the 2 methods was determined by Weighted Deming regression



Method Comparison	N	Intercept	Intercept 95% Confidence Interval	Slope	Slope 95% Confidence Interval	Correlation Coefficient	Sample Range IU/mL
VITROS 5600 vs Comparative Method	150	0.019	-0.029 to 0.066	0.99	0.986 to 0.999	0.999	0.935-438

j. Matrix comparison:

Specimens Recommended

- Serum

k. Conversion Factor Change

A study published in Clinica Chimica Acta 96 (1979) 59-65)[1] established the correspondence between the international unit defining activity of the WHO standard (I.U.) and the mass units as 1 I.U.= 1.21 ng of AFP (CI=1.02-1.43). The standard preparation has been investigated in two collaborative studies using several Reagent Pack methods, such as radioimmunoassay, single radial immunodiffusion and immunoelectrophoresis.[1, 2] Six laboratories estimated that one IU approximately equals 1.21 (1.02 – 1.43) nanograms of AFP[1] .

For the Predicate VITROS AFP Reagent Pack AFP concentrations are quoted in IU/mL or ng/mL. Conversion between units is made using the formula: result in ng/mL= result in IU/mLx1.04.

Efforts to harmonize this conversion factor between manufacturers are ongoing and the National Cancer Institute is using the 1.21 conversion factor. The adoption of the 1.21 conversion factor aligns the modified VITROS AFP Reagent Pack to the other manufacturers already using the 1.21 conversion factor.

Unit Conversion for the predicate VITROS AFP Reagent Pack

Alternate
ng/mL (IU/mL× 1.04*)

Unit Conversion for the modified VITROS AFP Reagent Pack

Alternate
ng/mL (IU/mL× 1.21*)

Customer communications will be issued with full details of any identified risks and mitigations.

Specimens Not Recommended

Do not use turbid specimens. Turbidity in specimens may affect test results.

3. Clinical studies:

a. Clinical Sensitivity:
Not applicable.

b. Clinical Specificity:
Not applicable.

c. Other clinical supportive data:
Not applicable.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

Same as K983031

N. Proposed Labeling: The labeling is sufficient, and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.