March 13, 2024

Siemens Healthcare Diagnostics Inc
Karlyn Kellogg
Regulatory Affairs Professional
Glyn Rhonwy, Llanberis
Caernarfon
Llanberis, Gwynedd LL55 4EL
United Kingdom

Re: K233946
Trade/Device Name: IMMULITE 2000 BR-MA
Regulation Number: 21 CFR 866.6010
Regulation Name: Tumor-Associated Antigen Immunological Test System
Regulatory Class: Class II
Product Code: MOI
Dated: December 14, 2023
Received: December 14, 2023

Dear Karlyn Kellogg:

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 (the 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 available 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.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device"

(https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

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 Part 803) for devices or postmarketing safety reporting (21 CFR Part 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 Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 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 -S

Ying Mao, Ph.D.
Branch Chief
Division of Immunology and Hematology Devices
OHT7: Office of In Vitro Diagnostics
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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)*
K233946

Device Name
IMMULITE 2000 BR-MA

Indications for Use *(Describe)*
For in vitro diagnostic use with the IMMULITE 2000 Systems Analyzers - for the quantitative measurement of CA15-3 antigen in human serum and plasma, as an aid in the detection of recurrence in previously treated stage II and stage III breast cancer patients, and in the management of metastatic breast cancer patients by monitoring disease progression or response to treatment. Serial testing for patient CA15-3 values should be used in conjunction with other clinical methods used for detecting early recurrence in stage II and stage III disease and for monitoring response to treatment in patients with metastatic breast 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.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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510(k) Summary

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

The assigned 510(k) number is: K233946

I. Submitter

Contact Person: Karlyn Kellogg
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Date of Preparation: March 6, 2024

II. Device

Trade Name:	IMMULITE® 2000 BR-MA
Common Name:	System, Test, Immunological, Antigen, Tumor
Classification Name:	Tumor-associated antigen immunological test system
Regulation Number:	21 CFR 866.6010
Classification:	Class II
Product Code:	MOI
Review Panel:	Immunology (82)

III. Predicate Device

The predicate device IMMULITE® 2000 BR-MA, manufactured by Siemens Healthcare Diagnostics Products Ltd, Glyn Rhonwy, Llanberis, Wales, United Kingdom, was cleared by the FDA under K013984.

IV. Device Description

The IMMULITE® 2000 BR-MA assay was cleared under K013984. The components of the cleared assay were modified to reduce biotin interference.

The modified IMMULITE® 2000 BR-MA Assay is comprised of the following components:

Component	Volume	Ingredients
BR-MA Bead Pack (L2BR12)	200 beads	Polystyrene bead coated with Ligand-labeled anti-CA15-3 murine monoclonal antibody
BR-MA Reagent Wedge (L2BRA2) – Well 1	11.5 mL	Serum-based buffer, with preservative
BR-MA Reagent Wedge (L2BRA2) – Well 2	11.5 mL	Alkaline phosphatase (bovine calf intestine) conjugated to murine monoclonal anti-CA15-3 antibody in buffer, with preservative
BR-MA Adjustors (LBRL, LBRH)	3 mL each	Lyophilized CA15-3 in a nonhuman serum matrix, with preservative (low and high levels)

The IMMULITE 2000 BR-MA is a solid-phase, two-step chemiluminescent immunometric assay. There are two incubation cycles of 30 minutes each.

During the initial 30-minute cycle, the patient sample is incubated with biotinylated antibody coated bead (bead pack) and a buffer (reagent wedge well 1). The biotinylated antibody on the bead captures the antigen in the patient sample. On completion of the first 30-minute cycle, unbound sample/buffer are then removed via a centrifugal wash.

During the second 30-minute cycle, alkaline phosphatase antibody conjugate in buffer (reagent wedge well 2) is added to complete the bead pair immunocomplex sandwich consisting of capture Ab-antigen-detection Ab. On completion of the second 30-minute cycle, unbound conjugate is removed by centrifugal wash. The amount of alkaline phosphatase bound is directly proportional to the analyte in the patient sample.

Following the two 30-minute incubation periods, IMMULITE chemiluminescent substrate (L2SUBM) is added for a further 5-minute incubation period to generate the luminogenic reaction.

The chemiluminescent substrate undergoes hydrolysis in the presence of the alkaline phosphatase to yield an unstable intermediate, which then emits photons. The sustained emissions are measured by the luminometer. The resulting relative light units are proportional to the concentration of CA15-3 in the sample, which is expressed as U/mL.

V. Intended Use / Indications for Use

For *in vitro* diagnostic use with the IMMULITE® 2000 Systems Analyzers – for the quantitative measurement of CA15-3 antigen in human serum and plasma, as an aid in the detection of recurrence in previously treated stage II and stage III breast cancer patients, and in the management of metastatic breast cancer patients by monitoring disease progression or response to treatment. Serial testing for patient CA15-3 values should be used in conjunction with other clinical methods used for detecting early recurrence in stage II and stage III disease and for monitoring response to treatment in patients with metastatic breast cancer.

VI. Comparison to Predicate Device

Comparison Table of Technological Characteristics

Attribute	**Candidate Device:** IMMULITE® 2000 BR-MA Assay, *modified*	**Predicate Device:** IMMULITE® 2000 BR-MA Assay, K013984
Intended Use / Indications for Use	For *in vitro* diagnostic use with the IMMULITE® 2000 Systems Analyzers – for the quantitative measurement of CA15-3 antigen in human serum and plasma, as an aid in the detection of recurrence in previously treated stage II and stage III breast cancer patients, and in the management of metastatic breast cancer patients by monitoring disease progression or response to treatment. Serial testing for patient CA15-3 values should be used in conjunction with other clinical methods used for detecting early recurrence in stage II and stage III disease and for monitoring response to treatment in patients with metastatic breast cancer.	Same
Analyte	Cancer Antigen 15-3	Same

Attribute	**Candidate Device:** IMMULITE® 2000 BR-MA Assay, *modified*	**Predicate Device:** IMMULITE® 2000 BR-MA Assay, K013984
Automated	Automated assay	Same
Measurement	Quantitative	Same
Sample Type	Human serum in plain tubes and Becton Dickinson SST® vacutainer; heparinized and EDTA plasma	Same
Detection Limit	Detection Limits: Limit of Blank (LoB) = 0.21 U/mL Limit of Detection (LoD) = 0.30 U/mL Limit of Quantitation (LoQ) = 1 U/mL LoB, LoD, and LoQ were determined in accordance with Clinical and Laboratory Standards Institute (CLSI) EP17-A2	Analytical Sensitivity: 1.0 U/mL
Assay Measuring Interval	1–300 U/mL	Same
Operating Principle	Immunologic sandwich	Same
Technology	Direct chemiluminescent	Same
Instrument	IMMULITE® 2000 Systems Analyzers	Same
Sample Volume	5 µL	Same
Calibrator (Adjustors)	Lyophilized CA15-3 in a nonhuman serum matrix, with preservative	Same
Controls	Commercially available, minimum of 2 levels	Same
Detection Antibody	Alkaline phosphatase (bovine calf intestine) conjugated to murine monoclonal anti-CA15-3 antibody	Same
Capture Antibody	Anti-CA15-3 murine monoclonal antibody	Same
Biotin Interference	Specimens that contain biotin at a concentration of 3500 ng/mL demonstrate a less than or equal to 10% change in results. Biotin concentrations greater than this may lead to incorrect results for patient samples.	Specimens that contain biotin at a concentration of 100 ng/mL demonstrate a less than or equal to 10% change in results. Biotin concentrations greater than this may lead to falsely depressed results for patient samples.

VII. Summary of Performance Testing

Substantial equivalence of the modified IMMULITE® 2000 BR-MA assay was demonstrated by testing performance characteristics including detection capability, linearity, method comparison, precision, recovery, interference, hook effect, reference range and matrix comparison.

The following performance data are provided in support of a substantial equivalence determination.

i. Detection Limits

Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) were determined in accordance with CLSI EP17-A2: *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition*. The LoB, LoD, and LoQ estimates are summarized below:

LoB	0.21 U/mL
LoD	0.30 U/mL
LoQ	1 U/mL

ii. Measuring Interval / Linearity

Linearity studies were conducted with 3 reagent lots consistent with the governing standard CLSI EP06-ED2: *Evaluation of the Linearity of Quantitative Measurement Procedures*.

A high sample pool and low sample were mixed to prepare a linearity panel of ten levels. Linearity was determined if the allowable deviation from linearity (ADL) was ≤ 15% at each individual level.

Linearity was confirmed across the assay range by acceptable ADL at each individual level and supports the measuring interval of 1 – 300 U/mL.

iii. Method Comparison: Quantitative Assay

The method comparison study was performed comparing the modified device to the currently marketed device. A total of 274 patient samples covering the full range of the assay were analyzed. A single replicate was processed for each sample. Passing-Bablok regression was used to compare the devices.

Lot	Specimen Type	Comparison Assay (x)	N	Regression Equation	Correlation Coefficient
1	Serum	IMMULITE 2000 BR-MA	274	Y = 0.98x + 0.71	0.989
2	Serum	IMMULITE 2000 BR-MA	274	Y = 0.99x + 0.16	0.992
3	Serum	IMMULITE 2000 BR-MA	274	Y = 1.04x - 0.79	0.990

iv. Verification of Assay Precision

Precision studies were conducted on one reagent lot on one IMMULITE 2000 analyzer in accordance with CLSI EP05-A3: *Evaluation of Precision of Quantitative Measurement Procedures*. Testing was performed on five serum samples spanning the range of the assay. Each sample was tested in duplicate over a period of 20 days, two runs per day, for a total of 40 runs and 80 replicates.

Level	Mean (U/mL)	Within-Run		Total (Within-Lab)	
		SD	%CV	SD	%CV
1	21.0	1.12	5.3	1.56	7.4
2	38.7	1.85	4.8	2.74	7.1
3	79.0	4.35	5.5	5.71	7.2
4	175	8.86	5.1	12.5	7.1
5	234	16.0	6.8	17.2	7.4

v. Verification of Assay Reproducibility

Reproducibility studies were conducted on three reagents lot on one IMMULITE 2000 analyzer in accordance with CLSI EP05-A3: *Evaluation of Precision of Quantitative Measurement Procedures*, using the 5 x 5 x 3 experimental design. Testing was performed on five serum samples spanning the range of the assay. Each sample was tested over a period of five days, with five replicates per sample.

Level	Mean (U/mL)	Total (Reproducibility)	
		SD	%CV
1	20.7	1.09	5.3
2	39.9	1.80	4.5
3	77.6	4.69	6.0
4	176	9.34	5.3
5	234	13.5	5.8

vi. Recovery

Spike and recovery studies were performed by spiking samples 1:19 (5% spike) with three CA15-3 solutions of differing concentrations.

Sample	Neat Sample Result (U/mL)	Spike Solution	Spiking solution concentration (U/mL)	Expected Value (U/mL)	Observed Value (U/mL)	% Recovery
S1	48	A	360	64	61	95%
		B	780	85	86	101%
		C	1520	122	128	105%
S2	87	A	360	101	99	98%
		B	780	122	116	95%
		C	1520	159	161	101%
S3	102	A	360	115	115	100%
		B	780	136	125	92%
		C	1520	173	172	99%
S4	132	A	360	143	145	101%
		B	780	164	169	103%
		C	1520	201	208	103%
S5	222	A	360	229	240	105%
		B	780	250	233	93%
		C	1520	287	283	99%

vii. Interference

Verification of the assay interference was conducted in accordance with CLSI EP07-ED3: *Interference Testing in Clinical Chemistry*.

The following substances tested were determined to have no significant interference:

Compound	Interferent Concentration
Hemoglobin	381 mg/dL
Conjugated Bilirubin	200 mg/L
Unconjugated Bilirubin	200 mg/L
Intralipid	3000 mg/dL
Biotin	3500 ng/mL
5-Fluorouracil	1000 µg/mL
Cisplatin	100 µg/mL
Cyclophosphamide	1000 µg/mL
Doxorubicin Hydrochloride	100 µg/mL
Mitomycin-C	100 µg/mL
Vincristine	1 µg/mL

The following substances tested were found to have no detectable specificity (cross-reactivity):

Compound	Cross-Reactant Concentration
Alpha-fetoprotein (AFP)	5,000 IU/mL
Cancer Antigen 125 (CA125)	10,000 U/mL
Cancer Antigen 19-9 (CA19-9)	2,000 U/mL
Carcinoembryonic Antigen (CEA)	5,000 ng/mL

viii. Hook Effect

No hook effect was observed up to 80,000 U/mL. CA15-3 concentrations as high as 80,000 U/mL will report as >300 U/mL.

ix. Verification of Reference Range

The reference range was verified by assaying apparently healthy female samples according to CLSI EP28-A3C: *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory*. The existing reference range (6.4 – 58 U/mL) was verified.

	Lot 1	Lot 2	Lot 3
n Normal Females	69	69	69
n Normal Females samples between 6.4 - 58 U/mL	65	65	65
% Normal Females samples between 6.4 - 58 U/mL	94%	94%	94%

Siemens provides this information for reference. As with all *in vitro* diagnostic assays, each laboratory should determine its own reference ranges for the diagnostic evaluation of patient results. Consider these values as a guideline only.

x. Matrix Comparison

The matrix comparison/specimen equivalence study was performed to evaluate the performance using different tube types (SST, Lithium Heparin, and EDTA). The study demonstrated comparable values to serum samples.

VIII. Conclusion

These performance studies support that the modified IMMULITE 2000 BR-MA Assay is substantially equivalent to the IMMULITE 2000 BR-MA Assay that is currently marketed, except for reduced biotin interference.