March 06, 2020

Leica Biosystems Newcastle Ltd.
% Zhijun (Julie) Pan
Manager, Regulatory Affairs and Submissions
Leica Biosystems
38 Cherry Hill Drive
Danvers, MA 01923

Re: K193393
Trade/Device Name: BOND Ready-to-Use Primary Antibody Progesterone Receptor (16), Novocastra Liquid Mouse Monoclonal Antibody Progesterone Receptor Clone 16 (Concentrated Liquid Antibody Format)
Regulation Number: 21 CFR 864.1860
Regulation Name: Immunohistochemistry Reagents And Kits
Regulatory Class: Class II
Product Code: MXZ
Dated: December 5, 2019
Received: December 6, 2019

Dear Zhijun (Julie) Pan:

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,

Soma Ghosh, Ph.D.
Chief
Molecular Pathology and Cytology Branch
Division of Molecular Genetics and Pathology
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K193393

Device Name
BOND Ready-to-Use Primary Antibody Progesterone Receptor (16),
Novocastra Liquid Mouse Monoclonal Antibody Progesterone Receptor Clone (16) (Concentrated Liquid Antibody Format)

Indications for Use *(Describe)*

Ready-to-Use Format

For in vitro diagnostic use.

BOND Ready-to-Use Primary Antibody Progesterone Receptor (16) is a monoclonal antibody intended to be used for the qualitative identification by light microscopy of human progesterone receptor in formalin-fixed, paraffin-embedded tissue by immunohistochemical staining using the automated BOND-MAX or BOND-III systems. Progesterone Receptor Clone (16) specifically binds to the progesterone receptor antigen located in the nucleus of progesterone receptor positive normal and neoplastic cells.

Progesterone Receptor Clone (16) is indicated as an aid in the management, prognosis and prediction of therapy outcome of breast cancer. The clinical interpretation of any staining or its absence should be complemented by morphological studies using proper controls and should be evaluated within the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Progesterone Receptor Clone (16) is optimized for use on the Leica Biosystems automated BOND-MAX or BOND-III systems using the BOND Polymer Refine Detection kit.

Concentrated Liquid Antibody Format

For in vitro diagnostic use.

Novocastra Liquid Mouse Monoclonal Antibody Progesterone Receptor Clone (16) (Concentrated Liquid Antibody Format) is intended to be used for the qualitative identification by light microscopy of human progesterone receptor in formalin-fixed, paraffin-embedded tissue by immunohistochemical staining. Progesterone Receptor Clone (16) specifically binds to the progesterone receptor antigen located in the nucleus of progesterone receptor positive normal and neoplastic cells.

Progesterone Receptor Clone (16) Monoclonal Antibody (Concentrated Liquid Antibody Format) is indicated as an aid in the management, prognosis and prediction of therapy outcome of breast cancer. The clinical interpretation of any staining or its absence should be complemented by morphological studies using proper controls and should be evaluated within the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

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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SECTION 5
510(k) SUMMARY

This Premarket Notification Submission (510(k)) Summary is prepared in accordance with 21 CFR 807.92.

I. Submitter Information

Sponsor Name:	Leica Biosystems Newcastle Ltd
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Contact Person:	Zhijun (Julie) Pan, MD, PhD, RAC Manager, Regulatory Affairs and Submissions Leica Biosystems
Contact Email:	Zhijun.pan@leicabiosystems.com
Contact Telephone:	978-578-5436
Date Summary Prepared:	November 22, 2019

II. Device

Trade (Proprietary) Name:	BOND Ready-to-Use Primary Antibody Progesterone Receptor (16), Novocastra Liquid Mouse Monoclonal Antibody Progesterone Receptor Clone (16) (Concentrated Liquid Antibody Format)
Common (Usual) Name:	Immunohistochemistry Assay, Antibody, Progesterone Receptor
Regulation Number:	21 CFR 864.1860
Regulation Name:	Immunohistochemistry reagents and kits
Regulatory Class:	II
Product Code:	MXZ
Product Panel:	88 (Pathology)

III. Predicate Device

Device Name:	BOND™ Ready-to-Use Primary Antibody Progesterone Receptor (16), Novocastra™ Liquid Mouse Monoclonal Antibody Progesterone Receptor Clone 16
Device 510(k):	k171753

IV. Device Description

Progesterone Receptor (16) is a mouse anti-human monoclonal antibody produced as a tissue culture supernatant. This antibody is utilized to perform a qualitative immunohistochemical (IHC) assay to identify Progesterone Receptor expression in human breast cancer tissue routinely processed and paraffin-embedded for histological examination.

Progesterone Receptor (PGR) Clone 16 Primary Antibody is provided in a Ready-to-Use (RTU) and a concentrated liquid format. The RTU format is supplied in Tris buffered saline with carrier protein, containing 0.35% ProClin™ 950 as a preservative and is provided in two volumes (7 mL and 30 mL). The total protein concentration is approximately 10 mg/mL and the total antibody concentration is greater than or equal to 1 mg/L as determined by ELISA. The RTU format is optimally diluted for use on the automated BOND-MAX and BOND-III instrument staining platforms in combination with BOND Polymer Refine Detection (DS9800). The concentrated liquid format is provided so that customers may utilize manual staining protocols. The concentrated liquid format is a liquid tissue culture supernatant containing 15 mM sodium azide as a preservative. The total protein concentration is determined on a per batch basis and is described on the vial label, and the antibody concentration is greater than or equal to 324.0 mg/L as determined by ELISA.

The BOND-MAX and BOND-III instruments are fully automated slide stainers that perform automated deparaffinization (dewaxing), antigen retrieval, immunohistochemistry (IHC) staining/*in situ* hybridization (ISH) staining, and counterstaining. The major components of the BOND staining platforms are the processing module, computer (BOND controller), handheld ID scanner, and slide label printer. The BOND staining platforms are composed of a number of discrete software components including the BOND application software, BOND instrument/processing module software, BOND service software, and Laboratory interface system - integration package (LIS-IP).

V. Intended Use

Ready-to-Use Format

For *in vitro* diagnostic use.

BOND Ready-to-Use Primary Antibody Progesterone Receptor (16) is a monoclonal antibody intended to be used for the qualitative identification by light microscopy of human progesterone receptor in formalin-fixed, paraffin-embedded tissue by immunohistochemical staining using the automated BOND-MAX or BOND-III systems. Progesterone Receptor Clone (16) specifically binds to the progesterone receptor antigen located in the nucleus of progesterone receptor positive normal and neoplastic cells.

Progesterone Receptor Clone (16) is indicated as an aid in the management, prognosis and prediction of therapy outcome of breast cancer. The clinical interpretation of any staining or its absence should be complemented by morphological studies using proper controls and should be evaluated within the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Progesterone Receptor Clone (16) is optimized for use on the Leica Biosystems automated BOND-MAX or BOND-III systems using the BOND Polymer Refine Detection kit.

Concentrated Liquid Antibody Format
For *in vitro* diagnostic use.
Novocastra Liquid Mouse Monoclonal Antibody Progesterone Receptor Clone (16) (Concentrated Liquid Antibody Format) is intended to be used for the qualitative identification by light microscopy of human progesterone receptor in formalin-fixed, paraffin-embedded tissue by immunohistochemical staining. Progesterone Receptor Clone (16) specifically binds to the progesterone receptor antigen located in the nucleus of progesterone receptor positive normal and neoplastic cells.

Progesterone Receptor Clone (16) Monoclonal Antibody (Concentrated Liquid Antibody Format) is indicated as an aid in the management, prognosis and prediction of therapy outcome of breast cancer. The clinical interpretation of any staining or its absence should be complemented by morphological studies using proper controls and should be evaluated within the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

VI. Comparison of Technological Characteristics with the Predicate Device

The BOND Ready-to-Use Primary Antibody Progesterone Receptor (16) and Novocastra Liquid Mouse Monoclonal Antibody Progesterone Receptor Clone 16 is substantially equivalent to its predicate device with the same name (except removal of the ™ trade mark), cleared under k171753. The subject device adds the BOND-III instrument staining platform and the BOND Ready-to-Use (RTU) Primary Antibody (30 mL) to the existing device. The similarities and differences between the subject device and the predicate device are summarized in **Table 1** below.

Table 1. Comparison of Technological Characteristics with the Predicate Device

Similarities		
Item	Subject Device	Predicate Device k171753
Intended Use	Qualitative identification of human Progesterone Receptor in breast cancer patients	Same
Antibody Type	Mouse monoclonal	Same
Isotype	IgG1	Same
PR Clone	16	Same
Immunogen	A prokaryotic recombinant protein corresponding to the N-terminal region of the A form of the human progesterone receptor	Same
Storage	2-8 °C	Same
Technology	Immunohistochemistry	Same

Tissue Type	Formalin-fixed paraffin-embedded breast cancer tissue	Same
Staining Pattern	Nuclear	Same
Staining Protocol	IHC Protocol F	Same
Differences		
Item	Subject Device	Predicate Device
Staining Instrument	BOND-III & BOND-MAX	BOND-MAX
RTU Antibody Progesterone Receptor (16) Configuration	7 mL & 30 mL	7 mL

VII. Performance Data

Immunoreactivity

The specificity of PR (16) was evaluated on 118 normal tissues cases. Characteristic staining was observed in the nuclei of cells that express high levels of the protein, a proportion of endometrial, cervical ovarian and myometrial cells, and normal breast ductal cells. Negative tissues included adrenal, bone marrow, brain (cerebellum), brain (cerebrum), esophagus, heart, liver, mesothelial cells, parathyroid, peripheral nerve, skeletal muscle, skin, small intestine, spleen, spinal cord, stomach, testis, thymus, and thyroid. Positive staining was also observed in occasional stromal cells of the bladder, lung and prostate, occasional lymphocytes in colon and rectum, acinar cells in salivary/submandibular gland, occasional renal tubular cells in the kidney, occasional hypophyseal cells of the pituitary and occasional islet cells of the pancreas.

PR (16) was evaluated on a range of tumor tissue cases. Intense staining was observed in fibroadenomas of the breast, an endometrioid adenocarcinoma of the ovary and a follicular papillary adenocarcinoma of the thyroid. Moderate staining was observed in a fibroblastic meningioma and a small cell carcinoma of the lung. Weak staining was observed in a malignant meningioma and a follicular carcinoma of the thyroid. Variable staining was observed in adenocarcinomas of the endometrium. The percentage of positive cells was low (1-10%) in the follicular papillary adenocarcinoma and follicular carcinoma of the thyroid, and high (>10%) in the fibroblastic meningioma, malignant meningioma, fibroadenomas of the breast, small cell carcinoma of the lung, endometrioid adenocarcinoma of the ovary and adenocarcinomas of the endometrium.

Precision (Repeatability & Reproducibility)

Intra-run Repeatability

Six unique breast tumor tissue cases were stained as part of intra-run repeatability testing. Of the six tissues, two had PR high expression (>10% tumor cells), 1 PR low expression (1-10% tumor cells), and 3 PR negative (<1% tumor cells). 9 slides were stained per case in two runs resulting in 54 assessments.

Results: The Overall Percent Agreement (OPA) was 96.2% (51/53; 95% CI: 87.2% to 99.0%), with Positive Percent Agreement (PPA) of 96.3% (26/27; 81.7% – 99.3%), and Negative Percent Agreement (NPA) of 96.2% (25/26; 81.1% – 99.3%).

Inter-day, Inter-instrument, Inter-lot Repeatability
27 unique breast tumor tissue cases were stained as part of inter-day, inter-instrument, and inter-lot repeatability testing. Of the 27 tissues, 9 had PR high expression (>10% tumor cells), 5 PR low expression (1-10% tumor cells), and 13 PR negative (<1% tumor cells). 18 slides were stained per case in 21 runs resulting in 486 assessments.

Results: Inter-day repeatability: The OPA was 98.8% (479/485; 95% CI: 97.3% - 99.4%), with PPA of 100% (198/198; 98.1% – 100%), and NPA of 97.9% (281/287; 95.5% – 99.0%). Inter-instrument repeatability: The OPA was 98.8% (479/485; 95% CI: 97.3% - 99.4%), with PPA of 100% (198/198; 98.1% – 100%), and NPA of 97.9% (281/287; 95.5% – 99.0%). Inter-lot repeatability: The OPA was 98.8% (479/485; 95% CI: 97.3% - 99.4%), with PPA of 100% (198/198; 98.1% – 100%), and NPA of 97.9% (281/287; 95.5% – 99.0%).

All repeatability testing met acceptance criteria.

Reproducibility
The Reproducibility Study was conducted at 3 sites over 5 non-consecutive days and a minimum of 20 calendar days on 135 unique FFPE breast tumor tissue cases and scored according to ASCO/CAP guidelines (≥1% cut-off) (Arch Pathol Lab Med. 2010; 134(6): 907-922) for a total of 1209 evaluations. **Table 2** details the results of inter-laboratory reproducibility of the assay. The average positive, negative, and overall agreement was 96.2%, 95.7%, and 95.9%, respectively, supporting the highly reproducible results of PR (16) staining using the BOND-III when used for the determination of PR status in a clinical setting.

Table 2. Inter-Laboratory Reproducibility Results for Each Site and All Sites

Laboratories	Measure	Number of Agreements	Number of Pairs	% Agreement	95% CI
Lab 1 vs. 2	APA	203	211	96.2%	[94.2% -98.0%]
	ANA	183	191	95.8%	[93.6% -97.7%]
	AOA	386	402	96.0%	[94.0% -97.8%]
Lab 1 vs. 3	APA	206	215	95.8%	[93.7% -97.6%]
	ANA	181	190	95.3%	[92.9% -97.3%]
	AOA	387	405	95.6%	[93.6% -97.5%]
Lab 2 vs. 3	APA	206	213.5	96.5%	[94.6% -98.2%]
	ANA	181	188.5	96.0%	[93.9% -97.9%]
	AOA	387	402	96.3%	[94.3% -98.0%]
All Labs	APA	615	639.5	96.2%	[94.5% -97.6%]
	ANA	545	569.5	95.7%	[93.9% -97.3%]
	AOA	1160	1209	95.9%	[94.3% -97.4%]

Each pathologist (1 per site) scored all stained slides prepared by each site. A total of 1215 slides (405 per pathologist) were scored. **Table 3** details the inter-observer reproducibility

between three pathologists. The average positive, negative, and overall agreement was 94.1%, 93.4% and 93.7%, respectively.

Table 3. Inter-Pathologist Reproducibility Results for Each Pathologist and All Pathologists

Pathologists	Measure	Number of Agreements	Number of Pairs	% Agreement	95% CI
Pathologist 1 vs. 2	APA	196	209	93.8%	[91.3% -96.0%]
	ANA	182	195	93.3%	[90.6% -95.7%]
	AOA	378	404	93.6%	[91.1% -95.8%]
Pathologist 1 vs. 3	APA	210	220	95.5%	[93.3% -97.3%]
	ANA	174	184	94.6%	[92.0% -96.7%]
	AOA	384	404	95.0%	[92.8% -97.0%]
Pathologist 2 vs. 3	APA	196	211	92.9%	[90.2% -95.3%]
	ANA	178	193	92.2%	[89.2% -94.8%]
	AOA	374	404	92.6%	[89.9% -95.0%]
All Pathologists	APA	602	640	94.1%	[92.0% -95.8%]
	ANA	534	572	93.4%	[91.1% -95.3%]
	AOA	1136	1212	93.7%	[91.7% -95.5%]

All reproducibility studies met acceptance criteria.

Method Comparison

PR (16) testing was performed at 3 sites on BOND-III (Subject Device) and BOND-MAX (Predicate Device) and scored according to ASCO/CAP guidelines (≥1% cut-off) (Arch Pathol Lab Med. 2010; 134(6): 907-922). The method comparison data are presented in **Table 4**. The positive, negative and overall agreement was 95.5%, 95.7% and 95.6%, respectively. These results indicate PR (16) staining using the BOND-III is comparable to PR (16) staining using the BOND-MAX.

Table 4. Agreement between Subject Device and Predicate Device

		Predicate Device		
		Negative	**Positive**	**Total**
Subject Device	**Negative**	222	10	**232**
	Positive	10	213	**223**
	Total	**232**	**223**	**455**

Positive Percent Agreement = 213/223 = 95.5% (95% CI: 91.9%-97.5%)
Negative Percent Agreement = 222/232 = 95.7% (95% CI: 92.2%-97.6%)

Overall Percent Agreement = 435/455 = 95.6% (95% CI: 93.3%-97.1%)

The method comparison study results met acceptance criteria.

Stability

The continued and additional real-time stability tests using three lots of the device and transport tests using one lot of the device were conducted to determine the shelf life of the reagent. Based on the testing, the product shelf-life is conservatively set at 18 months, and remains unchanged from the predicate device.

VIII. Conclusions

These study results demonstrated that BOND Ready-to-Use Primary Antibody Progesterone Receptor (16) and Novocastra Liquid Mouse Monoclonal Antibody Progesterone Receptor Clone 16 is substantially equivalent to the predicate device.