August 25, 2026

Ventana Medical Systems, Inc.
Kathy Kim
Sr. Regulatory Affairs Manager
1910 E. Innovation Park Dr.
Tucson, AZ 85755

Re: P990081/S060
Trade/Device Name: PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody
Product Code: MVC
Filed: March 25, 2026
Amended: August 19, 2026

Dear Kathy Kim:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody for expanding the indications to include identifying patients with gastroesophageal adenocarcinoma (GEA), including gastric, gastroesophageal junction, and esophageal adenocarcinoma, who are eligible for treatment with ZIIHERA.

Intended Use for the PATHWAY anti-HER2 (4B5) antibody is as follows:

> PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody (PATHWAY anti-HER2 (4B5) antibody) is a rabbit monoclonal antibody intended for laboratory use for the semi-quantitative detection of HER2 antigen by immunohistochemistry (IHC) in sections of formalin-fixed, paraffin-embedded breast carcinoma, biliary tract cancer (gallbladder adenocarcinoma, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma) and gastroesophageal adenocarcinoma (gastric, gastroesophageal junction and esophageal adenocarcinoma) tissue using the *ultra*View Universal DAB Detection Kit on a BenchMark ULTRA or BenchMark ULTRA PLUS instrument.
>
> The IHC device is indicated for identifying patients who are eligible for treatment with the following therapies in accordance with the approved therapeutic labeling:

Indication for use	HER2 Score	Therapy
Breast carcinoma	IHC 3+ or IHC 2+/ISH amplified	Herceptin®
Breast carcinoma	IHC 3+ or IHC 2+/ISH amplified	KADCYLA®

Indication for use	HER2 Score	Therapy
Breast carcinoma	IHC 3+ or ISH amplified [a]	ENHERTU® [b]
Breast carcinoma	IHC 0 with membrane staining, IHC 1+ or IHC 2+/ISH non-amplified	ENHERTU®
Biliary tract cancer [c]	IHC 3+	ZIIHERA®
Gastroesophageal adenocarcinoma [c]	IHC 3+ or IHC 2+/ISH amplified	ZIIHERA® in combination with fluoropyrimidine- and platinum-containing chemotherapy and tislelizumab-jsgr [d]
Gastroesophageal adenocarcinoma [c]	IHC 3+	ZIIHERA® in combination with fluoropyrimidine- and platinum-containing chemotherapy [d]

[a] See Scoring Convention section for use of ISH in context of the indication for use.

[b] See ENHERTU® product label for specific clinical circumstances guiding HER2 testing.

[c] Biliary tract cancer and gastroesophageal adenocarcinoma indications are only approved for use with BenchMark ULTRA instrument.

[d] See the ZIIHERA® product label for specific clinical circumstances guiding HER2 testing.

Test results should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

This product is intended for in vitro diagnostic (IVD) use.

Based upon the information submitted, the PMA supplement is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below. Although this letter refers to your product as a device, please be aware that some approved products may instead be combination products. The Premarket Approval Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm identifies combination product submissions.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to all other applicable requirements, including those governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at 18 months when stored at 2-8°C.

Continued approval of the PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. This report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the CDRH Portal. The Annual Report should indicate the beginning and ending date of the period covered by the report and must include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the PMA device, under 21 CFR 814.82(a)(9), the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

You have agreed to provide the following non-clinical information in a report, which may be followed by a PMA supplement where applicable.

1. Ventana Medical Systems, Inc. must provide supplementary data from a between-day (3 days) precision study for the PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody assay utilizing intended use specimens that reflect current clinical practice for the gastroesophageal adenocarcinoma (GEA) indication. The study must include an adequate number of biopsy specimens representing all three GEA tissue subtypes (gastric, gastroesophageal junction, and esophageal adenocarcinoma), evaluated at both the IHC 2+ and IHC 3+ cutoffs. The data from this study must be provided to confirm the precision of the assay across the specimen types commonly encountered in clinical practice.

2. Ventana Medical Systems, Inc. must provide data from re-reading the slides stained in the original interlaboratory reproducibility study to confirm the reproducibility of PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody assay for the gastroesophageal adenocarcinoma (GEA) indication at both the IHC 2+ and IHC 3+ cutoffs when a formal washout period between reading sets has been maintained. The slides must be read by a minimum of 3 pathologists not involved in the original interlaboratory reproducibility study, including case qualification and/or post-study evaluation. There must be an adequate washout period between reading sets (≥ 14 days). The data from this study must be provided to confirm the reproducibility of the assay across readers, sites, and days in the GEA intended use population.

The final study protocols, data, study conclusions, and any related labeling revisions should be submitted within 12 months of the PMA approval date.

Be advised that failure to comply with any post-approval requirement constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 21 CFR 814.46(a)(2).

This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final Unique Device Identification (UDI) rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR Part 830

Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. Combination Products may also be subject to UDI requirements (see 21 CFR 801.30). For more information on these requirements, please see the UDI website available at https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-udi-system.

Before making any change affecting the safety or effectiveness of the PMA device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. Additional information about changes that may require a PMA supplement are provided in the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" https://www.fda.gov/media/81431/download.

Your device is also subject to, among other requirements, the Quality Management System Regulation (QMSR) (21 CFR Part 820), which includes, but is not limited to, ISO 13485 clause 7.3 (Design controls), ISO 13485 clause 8.3 (Nonconforming product), ISO 13485 clause 8.5.2 (Corrective action), and ISO 13485 clause 8.5.3 (Preventative action). Please note that regardless of whether a change requires premarket review, the QMSR requires device manufacturers to review and approve changes to device design and production (ISO 13485 clause 7.3 and ISO 13485 clause 7.5) and document changes and approvals in the Medical Device File (ISO 13485 clause 4.2.3).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52 for devices or post-marketing safety reporting (21 CFR Part 4, Subpart B) for combination products, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems and on combination product post-marketing safety reporting is available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

In accordance with the recall requirements specified in 21 CFR 806.10 for devices or the post-marketing safety reporting requirements (21 CFR Part 4, Subpart B) for combination products, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may

present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/industry-guidance-recalls.

CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found at https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/pma-approvals. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with a copy of all final labeling. Final labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final labeling is identical to the labeling approved in draft form. If the final labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted to the CDRH Portal and should reference the above PMA number to facilitate processing. For more information on the CDRH Portal, please visit https://www.fda.gov/medical-devices/industry-medical-devices/send-and-track-medical-device-premarket-submissions-online-cdrh-portal.

If you have any questions concerning this approval order, please contact Cara Carraher at Cara.Carraher@fda.hhs.gov.

Sincerely,

ZIVANA TEZAK-FRAGALE -S

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