



July 30, 2020

Roche Molecular Systems, Inc.
Rita Hoady
Senior Manager, Regulatory Affairs
4300 Hacienda Drive
Pleasanton, California 94588-2722

Re: DEN200015

Trade/Device Name: cobas EBV

Regulation Number: 21 CFR 866.3183

Regulation Name: Quantitative viral nucleic acid test for transplant patient management

Regulatory Class: Class II

Product Code: QLX

Dated: February 28, 2020

Received: March 2, 2020

Dear Rita Hoady:

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 cobas EBV, including the cobas EBV Control Kit and cobas Buffer Negative Control Kit, a prescription device with the following indications for use:

cobas EBV is an in vitro nucleic acid amplification test for the quantitation of Epstein-Barr virus (EBV) DNA in human EDTA plasma on the cobas 6800/8800 Systems.

cobas EBV is intended for use as an aid in the management of EBV in transplant patients. In patients undergoing monitoring of EBV, serial DNA measurements can be used to indicate the need for potential treatment changes and to assess response to treatment.

The results from cobas EBV are intended to be read and analyzed by a qualified licensed healthcare professional in conjunction with clinical signs and symptoms and relevant laboratory findings.

Negative test results do not preclude EBV infection or EBV disease. Test results must not be the sole basis for patient management decisions.

cobas EBV is not intended for use as a screening test for donors of blood or blood products or human cells, tissues, and cellular and tissue-based products (HCT/Ps).

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. FDA concludes that this device should be classified into Class II. This order, therefore, classifies the cobas EBV and substantially equivalent devices of this generic type, into Class II under the generic name Quantitative viral nucleic acid tests for transplant patient management.

FDA identifies this generic type of device as:

Quantitative viral nucleic acid test for transplant patient management. A quantitative viral nucleic acid test for transplant patient management is identified as a device intended for prescription use in the detection of viral pathogens by measurement of viral deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) using specified specimen processing, amplification, and detection instrumentation. The test is intended for use as an aid in the management of transplant patients with active viral infection or at risk for developing viral infections. The test results are intended to be interpreted by qualified healthcare professionals in conjunction with other relevant clinical and laboratory findings.

Section 513(f)(2) of the 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 March 2, 2020, FDA received your De Novo requesting classification of the cobas EBV. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the cobas EBV 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 cobas EBV 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:

Identified Risk	Mitigation Measures
Risk of false results	Certain warnings, limitations, results interpretation information, and explanation of procedures in labeling. Certain device descriptions and specifications, analytical studies, clinical studies, and risk analysis in design verification and validation.
Failure to correctly interpret test results	Certain warnings, limitations, results interpretation information, and explanation of procedures in labeling.

Identified Risk	Mitigation Measures
Failure to correctly operate the device	Certain warnings, limitations, results interpretation information, and explanation of procedures in labeling.

In combination with the general controls of the FD&C Act, the quantitative viral nucleic acid test for transplant patient management is subject to the following special controls:

1. The labeling required under 21 CFR 809.10(b) must include:
 - i. A prominent statement that the device is not intended for use as a donor screening test for the presence of viral nucleic acid in blood or blood products.
 - ii. Limitations which must be updated to reflect current clinical practice. These limitations must include, but are not limited to, statements that indicate:
 - A. Test results are to be interpreted by qualified licensed healthcare professionals in conjunction with clinical signs and symptoms and other relevant laboratory results
 - B. Negative test results do not preclude viral infection or tissue invasive viral disease and that test results must not be the sole basis for patient management decisions.
 - iii. A detailed explanation of the interpretation of results and acceptance criteria must be provided and include specific warnings regarding the potential for variability in viral load measurement when samples are measured by different devices. Warnings must include the following statement, where applicable: "Due to the potential for variability in [analyte] measurements across different [analyte] assays, it is recommended that the same device be used for the quantitation of [analyte] when managing individual patients."
 - iv. A detailed explanation of the principles of operation and procedures for assay performance.
2. Design verification and validation must include the following:
 - i. Detailed documentation of the device description, including all parts that make up the device, ancillary reagents required for use with the assay but not provided, an explanation of the methodology, design of the primer/probe sequences, rationale for the selected gene target, and specifications for amplicon size, guanine-cytosine content, and degree of nucleic acid sequence conservation. The design and nature of all primary, secondary and tertiary quantitation standards used for calibration must also be described.
 - ii. A detailed description of the impact of any software, including software applications and hardware-based devices that incorporate software, on the device's functions.

- iii. Documentation and characterization (e.g., determination of the identity, supplier, purity, and stability) of all critical reagents and protocols for maintaining product integrity throughout its labeled shelf-life.
- iv. Stability data for reagents provided with the device and indicated specimen types, in addition to the basis for the stability acceptance criteria at all time points chosen across the spectrum of the device's indicated life cycle, which must include a time point at the end of shelf life.
- v. All stability protocols, including acceptance criteria.
- vi. Final lot release criteria along with documentation of an appropriate justification that lots released at the extremes of the specifications will meet the claimed analytical and clinical performance characteristics as well as the stability claims.
- vii. Risk analysis and documentation demonstrating how risk control measures are implemented to address device system hazards, such as Failure Mode 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 viral stains (e.g., regular review of published literature and annual *in silico* analysis of target sequences to detect possible primer or probe mismatches). All results of this protocol, including any findings, must be documented.
- viii. Analytical performance testing that includes:
 - A. Detailed documentation of the following analytical performance studies: limit of detection, upper and lower limits of quantitation, inclusivity, precision, reproducibility, interference, cross reactivity, carry-over, quality control, specimen stability studies, and additional studies as applicable to specimen type and intended use for the device.
 - B. Identification of the viral strains selected for use in analytical studies, which must be representative of clinically relevant circulating strains.
 - C. Inclusivity study results obtained with a variety of viral genotypes as applicable to the specific assay target and supplemented by *in silico* analysis.
 - D. Reproducibility studies that include the testing of three independent production lots.
 - E. Documentation of calibration to a reference standard that FDA has determined is appropriate for the quantification of viral DNA or RNA (e.g., a recognized consensus standard).
 - F. Documentation of traceability performed each time a new lot of the standardized reference material to which the device is traceable is released, or when the field transitions to a new standardized reference material.
- ix. Clinical performance testing that includes:

- A. Detailed documentation from either a method comparison study with a comparator that FDA has determined is appropriate, or results from a prospective clinical study demonstrating clinical validity of the device.
- B. Data from patient samples, with an acceptable number of the virus-positive samples containing an analyte concentration near the lower limit of quantitation and any clinically relevant decision points. If an acceptable number of virus-positive samples containing an analyte concentration near the lower limit of quantitation and any clinically relevant decision cannot be obtained, contrived samples may be used to supplement sample numbers when appropriate, as determined by FDA.
- C. The method comparison study must include pre-defined maximum acceptable differences between the test and comparator method across all primary outcome measures in the clinical study protocol.
- D. The final release test results for each lot used in the clinical study.

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 quantitative viral nucleic acid tests for transplant patient management 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 Parts 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 Silke Schlottmann at 301-796-9551.

Sincerely,

for

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