Cepheid
Wei Zhang
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June 27, 2024

Re: DEN240016
Trade/Device Name: Xpert HCV; GeneXpert Xpress System
Regulation Number: 21 CFR 866.3171
Regulation Name: Simple point-of-care nucleic acid-based hepatitis C virus ribonucleic acid test
Regulatory Class: Class II
Product Code: SBP
Dated: April 15, 2024
Received: April 16, 2024

Dear Wei Zhang:

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 Xpert HCV; GeneXpert Xpress System, a prescription device with the following indications for use:

> The Xpert HCV test, performed on the GeneXpert Xpress System, is an automated in vitro reverse transcription polymerase chain reaction (RT-PCR) test for the qualitative detection of Hepatitis C Virus (HCV) RNA in human fingerstick K2-EDTA whole blood from adult individuals at risk and/or with signs and symptoms of HCV infection with or without antibody evidence of HCV infection. Detection of HCV RNA indicates that the virus is replicating and therefore is evidence of active infection. Detection of HCV RNA does not discriminate between acute and chronic states of infection.
>
> The Xpert HCV test is not intended for monitoring patients undergoing treatment or for use in screening blood, plasma, or tissue donors.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Xpert HCV; GeneXpert Xpress System, and substantially equivalent devices of this generic type, into Class II under the generic name simple point-of-care nucleic acid-based hepatitis C virus ribonucleic acid test.

FDA identifies this generic type of device as:

> **Simple point-of-care nucleic acid-based hepatitis C virus ribonucleic acid test**. A simple point-of-care nucleic acid-based hepatitis C virus (HCV) ribonucleic acid (RNA) test is an in vitro diagnostic device that is intended for prescription use for the detection of HCV RNA in clinical

specimens as an aid in the diagnosis of HCV infection or as an aid in the management of HCV-infected patients, including individuals without antibodies to HCV. This device is simple to use and does not involve sample manipulation, transportation of the sample to another functional area (e.g., a central laboratory or other specialized area), or measurement of reagents or analytes that could be affected by conditions such as sample turbidity or cell lysis. The test is not intended for use as a donor screening test for the presence of HCV RNA in blood, blood products, or tissue donors.

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 April 16, 2024, FDA received your De Novo requesting classification of the Xpert HCV; GeneXpert Xpress System. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Xpert HCV; GeneXpert Xpress System 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 Xpert HCV; GeneXpert Xpress System 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 to health are risk of false results, failure to correctly interpret the results, failure to correctly operate the device, and exposure to test samples. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Identified Risks to Health	Mitigation Measures
Risks of false test results	Certain labeling information, including limitations, device descriptions, explanation of procedures, and results interpretation information. Certain design verification and validation information, certain analytical studies and clinical studies, risk analysis strategies, lot release criteria, flex studies, and stability studies.
Failure to correctly interpret the results	Certain labeling information, including limitations, device descriptions, explanation of procedures, and results interpretation information.

Identified Risks to Health	Mitigation Measures
	Certain design verification and validation information, including critical reagent information, risk analysis strategies, lot release criteria, flex studies, and stability studies and protocols.
Failure to correctly operate the device	Certain labeling information, including limitations, device descriptions, and explanation of procedures. Certain design verification and validation information including critical reagent information, risk analysis strategies, lot release criteria, flex studies, and stability studies.

In combination with the general controls of the FD&C Act, the simple point-of-care nucleic acid-based HCV RNA test is subject to the following special controls:

(1) Any sample collection device used must be FDA-cleared, -approved, or -classified as 510(k) exempt (standalone or as part of a test system) for the collection of the sample types with which this device is intended to be used; alternatively, the sample collection device must be cleared in a premarket submission as a part of this device.
(2) The labeling required under 21 CFR 809.10(b) must include:
    (i) A prominent statement that the test is not intended for use as a donor screening test for the presence of HCV RNA from human cells, tissues, and cellular and tissue-based products;
    (ii) A detailed explanation of the principles of operation and procedures for performing the assay;
    (iii) Detailed descriptions of the performance characteristics of the device for each specimen type identified in the intended use based on the required analytical and clinical studies;
    (iv) A brief reference sheet (Quick Reference Instructions) for the intended user(s) that includes the name and intended use of the test, step-by-step instructions of all control and sample testing procedures for the identified specimen types, the result(s) interpretation recommendations, warnings and limitation statements, and information for troubleshooting or technical assistance with the device; and
    (v) Limitations, which must be updated to reflect current clinical practice and disease presentation and management. These limitations must include statements that indicate:
        (A) The specimen types for which the device has been cleared and that use of this test kit with specimen types other than those specifically cleared for this device may result in inaccurate test results.
        (B) When applicable, that assay performance characteristics have not been established in populations of immunocompromised or immunosuppressed patients, or other populations where test performance may be affected.
        (C) Erroneous test results may occur from improper specimen collection, technical error, or if the analyte level in the specimen is below the sensitivity of the test.
        (D) Test results are to be interpreted by qualified licensed healthcare professionals in conjunction with the individual's clinical presentation, history, and other laboratory results.
        (E) A prominent statement that the test is not for use in screening blood, blood products, or tissue donors.

(3) Design verification and validation must include:
   (i) Detailed device description, including the device components, ancillary reagents required but not provided, and an explanation of the device methodology. Additional information appropriate to the technology must be included, such as design of primers and probes, rationale for the selected gene targets, specifications for amplicon size, and degree of nucleic acid sequence conservation.
   (ii) For devices with assay calibrators, the design and composition of all primary, secondary, and subsequent quantitation standards used for calibration as well as their traceability to a standardized reference material that FDA has determined is appropriate (e.g., a recognized consensus standard). In addition, analytical testing must be performed following the release of a new lot of the standard material that was used for device clearance or approval, or when there is a transition to a new calibration standard.
   (iii) Documentation and characterization (e.g., determination of the identity, supplier, purity, and stability) of all critical reagents (including nucleic acid sequences for primers and probes) and protocols for maintaining product integrity.
   (iv) Detailed documentation of analytical performance studies conducted as appropriate to the technology, specimen types tested, and intended use of the device, including, but not limited to: limit of detection (LoD), precision, endogenous and exogenous interferences, cross reactivity, carryover, matrix equivalency, and sample and reagent stability. Samples selected for use in analytical studies or used to prepare samples for use in analytical studies must be from subjects with clinically relevant circulating genotypes in the United States. Cross-reactivity studies must include samples from HCV RNA negative subjects with other causes of liver disease, including autoimmune hepatitis, alcoholic liver disease, chronic hepatitis B virus, primary biliary cirrhosis, and nonalcoholic steatohepatitis, when applicable. The effect of each identified nucleic-acid isolation and purification procedure on detection must be evaluated.
   (v) Risk analysis and management strategies, such as Failure Modes Effects Analysis and/or Hazard Analysis and Critical Control Points summaries and their impact on test performance. This must include detailed documentation that demonstrates the effectiveness of risk control measures and device robustness, including the entire testing procedure from sampling to result interpretation, based on results from the following studies, as applicable per the intended use of the test device: human factors engineering (e.g., usability studies and user label comprehension) and flex studies.
   (vi) Final release criteria to be used for manufactured test lots with appropriate evidence that lots released at the extremes of the specifications will meet the identified analytical and clinical performance characteristics as well as the stability.
   (vii) Multisite reproducibility study that includes the testing of three independent production lots.
   (viii) All stability protocols, including acceptance criteria.
   (ix) Final release test results for each lot used in clinical studies.
   (x) Lot-to-lot precision studies, as appropriate.

(4) For devices intended for the qualitative detection of HCV RNA, in addition to the special controls listed in paragraphs (b)(1), (2), and (3) of this section, the design verification and validation must include detailed documentation of performance from a multisite clinical study. The clinical study must be consistent with and support the intended use population and intended operators (as applicable), must be conducted in a representative intended use setting, and must be adequately powered with sufficient numbers of HCV infected or non-infected subjects. Performance must be analyzed using an FDA

accepted comparator or patient infected status. This study must be conducted using appropriate patient samples.

(5) For devices intended for the quantitative detection of HCV RNA, in addition to the special controls listed in paragraphs (b)(1), (2), and (3) of this section, design verification and validation must include:
   (i) Detailed documentation of the following analytical performance studies conducted as appropriate to the technology, specimen types tested, and intended use of the device, including but not limited to: LoD, Upper Limit of Quantitation (ULoQ), Lower Limit of Quantitation (LLoQ), and linearity. LoD, LLoQ, and linearity studies must demonstrate acceptable device performance with all HCV genotypes detected by the device.
   (ii) Detailed documentation and data from a prospective multisite clinical study conducted that is consistent with and supports the intended use population and intended operators (as applicable) and that is conducted in a representative intended use setting.

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.

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 simple point-of-care nucleic acid-based HCV RNA test 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 Part 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 Maria Esteve-Gasent at maria.esteve-gasent@fda.hhs.gov.

Sincerely,

Uwe Scherf -S

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