DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center W066-G609
Silver Spring, MD 20993-0002

Cepheid
c/o Dr. Kerry Flom
904 Caribbean Drive
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July 25, 2013

Re: K131706 - Order for Granting the Request for *De Novo* Classification
Xpert® MTB/RIF Assay
Evaluation of Automatic Class III Designation-*De Novo* Request
Regulation Number: 21 CFR 866.3373
Regulation Name: Nucleic acid-based *in vitro* diagnostic devices for the detection of *Mycobacterium tuberculosis* complex and the genetic mutations associated with *Mycobacterium tuberculosis* complex antibiotic resistance in respiratory specimens
Regulatory Classification: Class II (special controls)
Product Code: PEU
Dated: June 12, 2013
Received: June 13, 2013

Dear Dr. Flom:

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® MTB/RIF Assay. The intended use is stated as:

> The Xpert® MTB/RIF Assay, performed on the GeneXpert® Instrument Systems, is a qualitative, nested real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for the detection of *Mycobacterium tuberculosis* complex DNA in raw sputum or concentrated sediments prepared from induced or expectorated sputum. In specimens where *Mycobacterium tuberculosis* complex (MTB-complex) is detected, the Xpert MTB/RIF Assay also detects the rifampin-resistance associated mutations of the *rpoB* gene.
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> The Xpert MTB/RIF Assay is intended for use with specimens from patients for whom there is clinical suspicion of tuberculosis (TB) and who have received no antituberculosis therapy, or less than 3 days of therapy. This test is intended as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings.
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> The Xpert MTB/RIF Assay does not provide confirmation of rifampin susceptibility since mechanisms of rifampin resistance other than those detected by this device may exist that may be associated with a lack of clinical response to treatment.
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> Specimens that have both MTB-complex DNA and rifampin-resistance associated mutations of the *rpoB* gene detected by the Xpert MTB/RIF Assay must have results confirmed by a reference laboratory. If the presence of rifampin-resistance

associated mutations of the *rpoB* gene is confirmed, specimens should also be tested for the presence of genetic mutations associated with resistance to other drugs.

The Xpert MTB/RIF Assay must be used in conjunction with mycobacterial culture to address the risk of false negative results and to recover the organisms for further characterization and drug susceptibility testing.

The Xpert MTB/RIF Assay should only be performed in laboratories that follow safety practices in accordance with the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories publication and applicable state or local regulations.

The Xpert® MTB/RIF Assay is a prescription device under 21 CFR Part 801.109. FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II.

FDA identifies this generic type of device as follows: Nucleic acid-based *in vitro* diagnostic devices for the detection of *Mycobacterium tuberculosis* complex and the genetic mutations associated with *Mycobacterium tuberculosis* complex antibiotic resistance in respiratory specimens.

Nucleic acid-based *in vitro* diagnostic devices for the detection of *Mycobacterium tuberculosis* complex and the genetic mutations associated with *Mycobacterium tuberculosis* complex antibiotic resistance in respiratory specimens are qualitative nucleic acid-based devices that detect the presence of *Mycobacterium tuberculosis* complex-associated nucleic acid sequences in respiratory samples. These devices are intended to aid in the diagnosis of pulmonary tuberculosis and the selection of an initial treatment regimen when used in conjunction with clinical findings and other laboratory results. These devices do not provide confirmation of antibiotic susceptibility since other e mechanisms of resistance may exist that may be associated with a lack of clinical response to treatment other than those detected by the device.

Section 513(f)(2) of the Federal 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 new 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, within 30 days of receiving notice of the NSE determination, request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. 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** classifying the device type.

On June 13, 2013, FDA filed your de novo request for classification of the Xpert® MTB/RIF Assay into class II. The petition was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Xpert® MTB/RIF Assay 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 the Xpert® MTB/RIF Assay intended for use as follows:

> The Xpert® MTB/RIF Assay, performed on the GeneXpert® Instrument Systems, is a qualitative, nested real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for the detection of *Mycobacterium tuberculosis* complex DNA in raw sputum or concentrated sediments prepared from induced or expectorated sputum. In specimens where *Mycobacterium tuberculosis* complex (MTB-complex) is detected, the Xpert MTB/RIF Assay also detects the rifampin-resistance associated mutations of the *rpoB* gene.
>
> The Xpert MTB/RIF Assay is intended for use with specimens from patients for whom there is clinical suspicion of tuberculosis (TB) and who have received no antituberculosis therapy, or less than 3 days of therapy. This test is intended as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings.
>
> The Xpert MTB/RIF Assay does not provide confirmation of rifampin susceptibility since mechanisms of rifampin resistance other than those detected by this device may exist that may be associated with a lack of clinical response to treatment.
>
> Specimens that have both MTB-complex DNA and rifampin-resistance associated mutations of the *rpoB* gene detected by the Xpert MTB/RIF Assay must have results confirmed by a reference laboratory. If the presence of rifampin-resistance associated mutations of the *rpoB* gene is confirmed, specimens should also be tested for the presence of genetic mutations associated with resistance to other drugs.

The Xpert MTB/RIF Assay must be used in conjunction with mycobacterial culture to address the risk of false negative results and to recover the organisms for further characterization and drug susceptibility testing.

The Xpert MTB/RIF Assay should only be performed in laboratories that follow safety practices in accordance with the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories publication and applicable state or local regulations.

can be classified in class II with the establishment of special controls for this type of device. FDA believes that the class II special controls identified later in this order, along with the applicable general controls, provide reasonable assurance of the safety and effectiveness of the device type.

Table: Potential Risks and Mitigations

Identified Risks	Mitigation Measures
False positive test results for the presence of *Mycobacterium tuberculosis* complex may lead to incorrect treatment of the individual with possible adverse effects. The patient may be subjected to unnecessary isolation. Unnecessary contact investigations may also occur.	The FDA document entitled "Class II Special Controls Guideline: Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of *Mycobacterium tuberculosis* Complex and Genetic Mutations Associated with Antibiotic Resistance in Respiratory Specimens," which addresses this risk through device description, performance studies, and labeling.
False negative test results for the presence of *Mycobacterium tuberculosis* complex could contribute to disease progression and increase the risk of transmitting disease to others.	The FDA document entitled "Class II Special Controls Guideline: Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of *Mycobacterium tuberculosis* Complex and Genetic Mutations Associated with Antibiotic Resistance in Respiratory Specimens," which addresses this risk through device description, performance studies, and labeling.
False positive test results for the presence of the genetic mutations associated with *Mycobacterium tuberculosis* complex antibiotic resistance may lead to incorrect treatment of the individual with possible adverse effects. The patient may be subjected to unnecessary isolation. Unnecessary contact investigations may also occur.	The following items: i) The device must include an external positive assay control as appropriate. Acceptable positive assay controls include *Mycobacterium tuberculosis* complex isolates containing one or more antibiotic-resistance associated target sequences detected by the device. ii) The device must include internal controls as appropriate. An acceptable internal control may include human nucleic acid co-extracted

	with *Mycobacterium tuberculosis* complex containing nucleic acid sequences associated with antibiotic resistance and primers amplifying human housekeeping genes (e.g., RNaseP, β-actin). iii) The device's intended use must include a description of the scope of antibiotic resistance targeted by the assay, i.e., the specific drugs and/or drug classes. iv) The specific performance characteristics section of the device's labeling must include information regarding the specificity of the assay oligonucleotides for detecting mutations associated with antibiotic resistance of *Mycobacterium tuberculosis* complex, and any information indicating the potential for non-specific binding (e.g., BLAST search). v) In demonstrating device performance you must perform: *A)* Pre-analytical studies that evaluate: *1)* If there is use of any frozen samples in the device performance studies, or if there is a device claim for the use of frozen samples for testing, the effect of freezing samples prior to testing and the effect of multiple freeze/thaw cycles on both antibiotic susceptible and antibiotic resistant strains of *Mycobacterium tuberculosis* complex. *2)* Nucleic acid extraction methods. Extraction methods must parallel those used in devices for the detection of *Mycobacterium tuberculosis* complex nucleic acid, and confirm that the detection of the genetic mutations associated with antibiotic resistance is not affected. *B)* Analytical studies that analyze: *1)* Limit of Detection. Limit of Detection must be determined in the most challenging matrix (e.g., sputum) claimed for use with the device. The Limit of Detection must be determined using both antibiotic susceptible and antibiotic resistant strains of *Mycobacterium tuberculosis* complex. The antibiotic

	resistant strains must be those with well characterized genetic mutations associated with antibiotic resistance. *2)* Analytical Reactivity (Inclusivity). Testing must be conducted to evaluate the ability of the device to detect genetic mutations associated with antibiotic resistance in a diversity of *Mycobacterium tuberculosis* complex strains. Isolates used in testing must be well characterized. Isolate strain characterization must be determined using standardized reference methods recognized by a reputable scientific body and appropriate to the strain lineage. *3)* Within-Laboratory (Repeatability) Precision Testing. Within-laboratory precision studies, if appropriate, must include at least one antibiotic resistant and one antibiotic susceptible strain of *Mycobacterium tuberculosis* complex. *4)* Between Laboratory Reproducibility Testing. The protocol for the reproducibility study may vary slightly depending on the assay format; however, the panel must include at least one antibiotic resistant and one antibiotic susceptible strain of *Mycobacterium tuberculosis* complex. *C)* Clinical Studies. Clinical performance of the device must be established by conducting prospective clinical studies that include subjects with culture confirmed active tuberculosis. Studies must attempt to enroll subjects at risk for antibiotic-resistant *Mycobacterium tuberculosis* complex; however, it may be necessary to include supplemental antibiotic resistant retrospective and contrived samples. Clinical studies must compare device results to both phenotypic drug susceptibility testing and genotypic reference methods. The genotypic reference method must be a polymerase chain reaction based method that uses primers different from those in the experimental device and confirmed by bi-directional sequencing.

False negative test results for the presence of the genetic mutations associated with *Mycobacterium tuberculosis* complex antibiotic resistance could contribute to disease progression and increase the risk of transmitting disease to others.	The following items: i) The device must include an external positive assay control as appropriate. Acceptable positive assay controls include *Mycobacterium tuberculosis* complex isolates containing one or more antibiotic-resistance associated target sequences detected by the device. ii) The device must include internal controls as appropriate. An acceptable internal control may include human nucleic acid co-extracted with *Mycobacterium tuberculosis* complex containing nucleic acid sequences associated with antibiotic resistance and primers amplifying human housekeeping genes (e.g., RNaseP, β-actin). iii) The device's intended use must include a description of the scope of antibiotic resistance targeted by the assay, i.e., the specific drugs and/or drug classes. iv) The specific performance characteristics section of the device's labeling must include information regarding the specificity of the assay oligonucleotides for detecting mutations associated with antibiotic resistance of *Mycobacterium tuberculosis* complex, and any information indicating the potential for non-specific binding (e.g., BLAST search). v) In demonstrating device performance you must perform: *A)* Pre-analytical studies that evaluate: *1)* If there is use of any frozen samples in the device performance studies, or if there is a device claim for the use of frozen samples for testing, the effect of freezing samples prior to testing and the effect of multiple freeze/thaw cycles on both antibiotic susceptible and antibiotic resistant strains of *Mycobacterium tuberculosis* complex. *2)* Nucleic acid extraction methods. Extraction methods must parallel those used in devices for the detection of *Mycobacterium tuberculosis* complex

	nucleic acid, and confirm that the detection of the genetic mutations associated with antibiotic resistance is not affected. *B)* Analytical studies that analyze: *1)* Limit of Detection. Limit of Detection must be determined in the most challenging matrix (e.g., sputum) claimed for use with the device. The Limit of Detection must be determined using both antibiotic susceptible and antibiotic resistant strains of *Mycobacterium tuberculosis* complex. The antibiotic resistant strains must be those with well characterized genetic mutations associated with antibiotic resistance. *2)* Analytical Reactivity (Inclusivity). Testing must be conducted to evaluate the ability of the device to detect genetic mutations associated with antibiotic resistance in a diversity of *Mycobacterium tuberculosis* complex strains. Isolates used in testing must be well characterized. Isolate strain characterization must be determined using standardized reference methods recognized by a reputable scientific body and appropriate to the strain lineage. *3)* Within-Laboratory (Repeatability) Precision Testing. Within-laboratory precision studies, if appropriate, must include at least one antibiotic resistant and one antibiotic susceptible strain of *Mycobacterium tuberculosis* complex. *4)* Between Laboratory Reproducibility Testing. The protocol for the reproducibility study may vary slightly depending on the assay format; however, the panel must include at least one antibiotic resistant and one antibiotic susceptible strain of *Mycobacterium tuberculosis* complex. *C)* Clinical Studies. Clinical performance of the device must be established by conducting prospective clinical studies that include subjects with culture confirmed active

	tuberculosis. Studies must attempt to enroll subjects at risk for antibiotic-resistant *Mycobacterium tuberculosis* complex; however, it may be necessary to include supplemental antibiotic resistant retrospective and contrived samples. Clinical studies must compare device results to both phenotypic drug susceptibility testing and genotypic reference methods. The genotypic reference method must be a polymerase chain reaction based method that uses primers different from those in the experimental device and confirmed by bi-directional sequencing.
Biosafety risks to healthcare workers handling specimens and control materials with the possibility of transmission of tuberculosis infection to healthcare workers	The FDA document entitled "Class II Special Controls Guideline: Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of Mycobacterium tuberculosis Complex and Genetic Mutations Associated with Antibiotic Resistance in Respiratory Specimens," which addresses this risk through labeling.

In addition to the general controls of the FD&C Act, a nucleic acid-based *in vitro* diagnostic devices for the detection of *Mycobacterium tuberculosis* complex and the genetic mutations associated with *Mycobacterium tuberculosis* complex antibiotic resistance in respiratory specimens is subject to the following special controls:

1) The FDA document entitled "Class II Special Controls Guideline: Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of *Mycobacterium tuberculosis* Complex and Genetic Mutations Associated with Antibiotic Resistance in Respiratory Specimens," which addresses the mitigation of risks specific to the detection of *M. tuberculosis* complex.

2) The following items, which address the mitigation of risks specific to the detection of the genetic mutations associated with antibiotic resistance of *Mycobacterium tuberculosis* complex:

   i) The device must include an external positive assay control as appropriate. Acceptable positive assay controls include *Mycobacterium tuberculosis* complex isolates containing one or more antibiotic-resistance associated target sequences detected by the device.

   ii) The device must include internal controls as appropriate. An acceptable internal control may include human nucleic acid co-extracted with *Mycobacterium tuberculosis* complex containing nucleic acid sequences associated with antibiotic resistance and primers amplifying human housekeeping genes (e.g., RNaseP, β-actin).

   iii) The device's intended use must include a description of the scope of antibiotic resistance targeted by the assay, i.e., the specific drugs and/or drug classes.

iv) The specific performance characteristics section of the device's labeling must include information regarding the specificity of the assay oligonucleotides for detecting mutations associated with antibiotic resistance of *Mycobacterium tuberculosis* complex, and any information indicating the potential for non-specific binding (e.g., BLAST search).

v) In demonstrating device performance you must perform:

A) Pre-analytical studies that evaluate:

1) If there is use of any frozen samples in the device performance studies, or if there is a device claim for the use of frozen samples for testing, the effect of freezing samples prior to testing and the effect of multiple freeze/thaw cycles on both antibiotic susceptible and antibiotic resistant strains of *Mycobacterium tuberculosis* complex.

2) Nucleic acid extraction methods. Extraction methods must parallel those used in devices for the detection of *Mycobacterium tuberculosis* complex nucleic acid, and confirm that the detection of the genetic mutations associated with antibiotic resistance is not affected.

B) Analytical studies that analyze:

1) Limit of Detection. Limit of Detection must be determined in the most challenging matrix (e.g., sputum) claimed for use with the device. The Limit of Detection must be determined using both antibiotic susceptible and antibiotic resistant strains of *Mycobacterium tuberculosis* complex. The antibiotic resistant strains must be those with well characterized genetic mutations associated with antibiotic resistance.

2) Analytical Reactivity (Inclusivity). Testing must be conducted to evaluate the ability of the device to detect genetic mutations associated with antibiotic resistance in a diversity of *Mycobacterium tuberculosis* complex strains. Isolates used in testing must be well characterized. Isolate strain characterization must be determined using standardized reference methods recognized by a reputable scientific body and appropriate to the strain lineage.

3) Within-Laboratory (Repeatability) Precision Testing. Within-laboratory precision studies, if appropriate, must include at least one antibiotic resistant and one antibiotic susceptible strain of *Mycobacterium tuberculosis* complex.

4) Between Laboratory Reproducibility Testing. The protocol for the reproducibility study may vary slightly depending on the assay format; however, the panel must include at least one antibiotic resistant and one antibiotic susceptible strain of *Mycobacterium tuberculosis* complex.

C) Clinical Studies. Clinical performance of the device must be established by conducting prospective clinical studies that include subjects with culture confirmed active tuberculosis. Studies must attempt to enroll subjects at risk for antibiotic-resistant *Mycobacterium tuberculosis* complex; however, it may be necessary to include supplemental antibiotic resistant retrospective and

contrived samples. Clinical studies must compare device results to both phenotypic drug susceptibility testing and genotypic reference methods. The genotypic reference method must be a polymerase chain reaction based method that uses primers different from those in the experimental device and confirmed by bi-directional sequencing.

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 nucleic acid-based *in vitro* diagnostic devices for the detection of *Mycobacterium tuberculosis* complex and the genetic mutations associated with *Mycobacterium tuberculosis* complex antibiotic resistance in respiratory specimens they intend to market and receive clearance to market from FDA prior to marketing the device.

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 market your device subject to the general control provisions of the FD&C Act and the special controls identified in this order.

If you have any questions concerning this classification order, please contact Janice Washington at 301-796-6207.

Sincerely yours,

Sally A. Hojvat -S

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