DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA–2014–N–1440]

Medical Devices; Immunology and Microbiology Devices; Classification of Nucleic Acid-Based Devices for the Detection of Mycobacterium Tuberculosis Complex and the Genetic Mutations Associated With Antibiotic Resistance

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying nucleic acid-based in vitro diagnostic devices for the detection of *Mycobacterium tuberculosis* complex (MTB-complex) and the genetic mutations associated with MTB-complex antibiotic resistance in respiratory specimens devices into class II (special controls). The Agency is classifying the device into class II (special controls) because special controls, in addition to general controls, will provide a reasonable assurance of safety and effectiveness of the device.

DATES: This order is effective November 21, 2014. The classification was applicable July 25, 2013.

FOR FURTHER INFORMATION CONTACT: Janice Washington, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 5554, Silver Spring, MD 20993–0002, 301–796–6207.

SUPPLEMENTARY INFORMATION:

I. Background

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(f)(1)), devices that were not in commercial distribution before May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976), generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless and until the device is classified or reclassified into class I or II, or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807) of the regulations.

Section 513(f)(2) of the FD&C Act, as amended by section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144), provides two procedures by which a person may request FDA to classify a device under the criteria set forth in section 513(a)(1) of the FD&C Act. Under the first procedure, the person submits a premarket notification under section 510(k) of the FD&C Act for a device that has not previously been classified and, within 30 days of receiving an order classifying the device into class III under section 513(f)(1) of the FD&C Act, the person requests a classification under section 513(f)(2). Under the second procedure, rather than first submitting a premarket notification under section 510(k) of the FD&C Act and then a request for classification under the first procedure, the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence and requests a classification under section 513(f)(2) of the FD&C Act. If the person submits a request to classify the device under this second procedure, FDA may decline to undertake the classification request if FDA identifies a legally marketed device that could provide a reasonable basis for review of substantial equivalence with the device or if FDA determines that the device submitted is not of ''low-moderate risk'' or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.

In response to a request to classify a device under either procedure provided by section 513(f)(2) of the FD&C Act, FDA will classify the device by written order within 120 days. This classification will 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 this classification.

On June 13, 2013, Cepheid submitted a request for de novo classification of the Xpert® MTB/RIF Assay under section 513(f)(2) of the FD&C Act.

In accordance with section 513(f)(2) of the FD&C Act, FDA reviewed the request for de novo classification in order to classify the device under the criteria for classification set forth in section 513(a)(1) of the FD&C Act. FDA classifies devices into class II if general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special 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 request, FDA determined that the device can be classified into class II with the establishment of special controls. FDA believes these special controls will provide reasonable assurance of the safety and effectiveness of the device.

The device is assigned the generic name nucleic acid-based in vitro diagnostic devices for the detection of MTB-complex and the genetic mutations associated with MTB-complex antibiotic resistance in respiratory specimens, and it is identified as qualitative nucleic acid-based devices that detect the presence of MTB-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 mechanisms of resistance may exist that may be associated with a lack of clinical response to treatment other than those detected by the device.

FDA has identified the following risks to health associated with this type of device and the measures required to mitigate these risks:

TABLE 1—IDENTIFIED RISKS TO HEALTH AND MITIGATION MEASURES

Identified risks to health	Mitigation measures
False positive test results for the presence of MTB-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 Mycobacterium tuberculosis Antibiotic Resistance in Respiratory Specimens,'' which addresses this risk through: Device Description Containing the Information Specified in the Special Control Guideline. Performance Studies. Labeling.
False negative test results for the presence of MTB-complex could contribute to disease progression and increase the risk of transmitting infection 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 Mycobacterium tuberculosis Antibiotic Resistance in Respiratory Specimens,'' which addresses this risk through: Device Description Containing the Information Specified in the Special Control Guideline. Performance Studies. Labeling.
False positive test results for the presence of genetic mutations associated with MTB-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.	§ 866.3373(b)(2) (21 CFR 866.3373(b)(2)), which addresses the mitigation of risks specific to the detection of the genetic mutations associated with antibiotic resistance of *M. tuberculosis* complex.
False negative test results for the presence of genetic mutations associated with MTB-complex antibiotic resistance could contribute to disease progression and increase the risk of transmitting antibiotic resistant tuberculosis to others.	§ 866.3373(b)(2), which addresses the mitigation of risks specific to the detection of the genetic mutations associated with antibiotic resistance of *M. tuberculosis* complex.
Biosafety risks to health care workers handling specimens and control materials with the possibility of transmission of tuberculosis infection to health care 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 Mycobacterium tuberculosis Antibiotic Resistance in Respiratory Specimens,'' which addresses this risk through: Labeling.

FDA believes that the measures set forth in the special controls guideline 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'' and the special controls identified in § 866.3373(b)(2) of this order are necessary, in addition to general controls, to mitigate the risks to health described in table 1.

Therefore, on July 25, 2013, FDA issued an order to the petitioner classifying nucleic acid-based in vitro diagnostic devices for the detection of MTB-complex and the genetic mutations associated with MTB-complex antibiotic resistance in respiratory specimens devices into class II. FDA is codifying this device type by adding § 866.3373.

II. 510(k) Premarket Notification

Following the effective date of this final classification order, any firm submitting a 510(k) premarket notification for this device type will need to comply with the special controls.

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. For this type of device, FDA has determined that premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device. Therefore, this type of device is not exempt from premarket notification requirements. Persons who intend to market this type of device must submit to FDA a premarket notification, prior to marketing the device, which contains information about the nucleic acid-based in vitro diagnostic devices for the detection of MTB-complex and the genetic mutations associated with MTB-complex antibiotic resistance in respiratory specimens they intend to market.

III. Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Paperwork Reduction Act of 1995

This final administrative order establishes special controls that refer to previously approved collections of information found in other FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The collections of information in 21 CFR parts 50 and 56 are approved under OMB control number 0910–0755; the collections of information in part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910–0120; the collections of information in 21 CFR part 812 are approved under OMB control number 0910–0078; the collections of information in 21 CFR part 820 have been approved under OMB control number 0910–0073; and the collections of information in 21 CFR part 801 and 21 CFR 809.10 have been approved under OMB control number 0910–0485.

List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 866 is amended as follows:

PART 866—IMMUNOLOGY AND MICROBIOLOGY DEVICES

■ 1. The authority citation for 21 CFR part 866 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

■ 2. Section 866.3373 is added to subpart D to read as follows:

§ 866.3373 Nucleic acid-based in vitro diagnostic devices for the detection of Mycobacterium tuberculosis complex (MTB-complex) and the genetic mutations associated with MTB-complex antibiotic resistance in respiratory specimens.

(a) *Identification.* Nucleic acid-based in vitro diagnostic devices for the detection of *Mycobacterium tuberculosis* complex (MTB-complex) and the genetic mutations associated with MTB-complex antibiotic resistance in respiratory specimens are qualitative nucleic acid-based devices that detect the presence of MTB-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 mechanisms of resistance may exist that may be associated with a lack of clinical response to treatment other than those detected by the device.

(b) *Classification.* Class II (special controls). The special controls for this device are:

(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 MTB-complex. For availability of the document, see § 866.1(e).

(2) The following items, which address the mitigation of risks specific to the detection of the genetic mutations associated with antibiotic resistance of MTB-complex:

(i) The device must include an external positive assay control as appropriate. Acceptable positive assay controls include MTB-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 MTB-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 MTB-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*) *Frozen samples.* 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 MTB-complex.

(*2*) *Nucleic acid extraction methods.* Extraction methods must parallel those used in devices for the detection of MTB-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 MTB-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 MTB-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 MTB-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 MTB-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 MTB-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 bidirectional sequencing.

Dated: October 15, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

37 CFR Parts 1, 2, 7, 11, 41, and 42

[Docket No.: PTO–P–2014–0045]

RIN 0651–AC98

Renaming of Express Mail® to Priority Mail Express®

AGENCY: United States Patent and Trademark Office, Commerce.

ACTION: Final rule.

SUMMARY: The United States Patent and Trademark (Office) is revising the rules of practice to change the phrase Express Mail or EXPRESS MAIL® to Priority Mail Express® due to the United States Postal Service (USPS) renaming Express Mail® to Priority Mail Express® on July 28, 2013, and to make other changes to conform the nomenclature used in the