



May 2, 2018

Curetis GmbH
c/o Gail Radcliffe, Ph.D.
Official Correspondent
Max-Eyth Strasse 42
Holzgerlingen, 71088 Germany

Re: DEN170047

Trade/Device Name: Unyvero LRT Application

Regulation Number: 21 CFR 866.3985

Regulation Name: Device to detect and identify microorganisms and associated resistance marker
nucleic acids directly in respiratory specimens

Regulatory Class: Class II

Product Code: QBH

Dated: September 8, 2017

Received: September 11, 2017

Dear Dr. Radcliffe:

This letter corrects our letter dated April 3, 2018.

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 Unyvero LRT Application, a prescription device with the following indications for use:

The Unyvero LRT Application is a qualitative nucleic acid multiplex test intended for the simultaneous detection and identification of nucleic acid sequences from the following microorganisms and antibiotic resistance markers in endotracheal aspirates from adult hospitalized patients with suspected lower respiratory tract infections.

Microorganism	Associated antibiotic resistance marker
<i>Acinetobacter</i> spp. ^a	<i>ctx-M</i> ^b , <i>kpc</i> , <i>ndm</i> , <i>oxa-23</i> , <i>oxa-24</i> , <i>oxa-58</i> , <i>vim</i>
<i>Chlamydia pneumoniae</i>	-
<i>Citrobacter freundii</i>	<i>ctx-M</i> ^b , <i>kpc</i> , <i>ndm</i> , <i>oxa-48</i> , <i>vim</i>
<i>Enterobacter cloacae</i> complex ^c	<i>ctx-M</i> ^b , <i>kpc</i> , <i>ndm</i> , <i>oxa-48</i> , <i>vim</i>
<i>Escherichia coli</i>	<i>ctx-M</i> ^b , <i>kpc</i> , <i>ndm</i> , <i>oxa-48</i> , <i>vim</i>
<i>Haemophilus influenzae</i>	<i>tem</i>
<i>Klebsiella oxytoca</i>	<i>ctx-M</i> ^b , <i>kpc</i> , <i>ndm</i> , <i>oxa-48</i> , <i>vim</i>
<i>Klebsiella pneumoniae</i> ^d	<i>ctx-M</i> ^b , <i>kpc</i> , <i>ndm</i> , <i>oxa-48</i> , <i>vim</i>
<i>Klebsiella variicola</i>	<i>ctx-M</i> ^b , <i>kpc</i> , <i>ndm</i> , <i>oxa-48</i> , <i>vim</i>
<i>Legionella pneumophila</i>	-
<i>Moraxella catarrhalis</i>	-
<i>Morganella morganii</i>	<i>ctx-M</i> ^b , <i>kpc</i> , <i>ndm</i> , <i>oxa-48</i> , <i>vim</i>
<i>Mycoplasma pneumoniae</i>	-
<i>Proteus</i> spp. ^e	<i>ctx-M</i> ^b , <i>kpc</i> , <i>ndm</i> , <i>oxa-48</i> , <i>vim</i>
<i>Pseudomonas aeruginosa</i>	<i>ctx-M</i> ^b , <i>kpc</i> , <i>ndm</i> , <i>vim</i>
<i>Serratia marcescens</i>	<i>ctx-M</i> ^b , <i>kpc</i> , <i>ndm</i> , <i>oxa-48</i> , <i>vim</i>
<i>Staphylococcus aureus</i>	<i>mecA</i>
<i>Stenotrophomonas maltophilia</i>	-
<i>Streptococcus pneumoniae</i>	-

^a *Acinetobacter* spp. includes: *A. baumannii*, *A. calcoaceticus*, *A. haemolyticus*, *A. junii*, *A. lwoffii*, *A. nosocomialis*, *A. parvus*, *A. pittii*, (detected by LRT Application) and *A. ursingii* (not detected by LRT Application).

^b *ctx-M*1 subgroup.

^c *Enterobacter cloacae* complex includes: *E. asburiae*, *E. cloacae*, *E. hormaechei*, *E. kobei*, *E. ludwigii*, and *E. xiangfangensis*.

^d *Klebsiella pneumoniae* includes two variants: *K. pneumoniae* (variant 1), and *K. quasipneumoniae* (variant 2)

^e *Proteus* spp. includes *P. hauseri*, *P. mirabilis*, *P. penneri* and *P. vulgaris*.

The Unyvero LRT Application performed on the Unyvero System is indicated as an aid in the diagnosis of lower respiratory tract infection in adult hospitalized patients with signs and symptoms of lower respiratory infection; results should be used in conjunction with other clinical and laboratory findings. As tracheal aspirates commonly contain colonizing microorganisms, detection of Unyvero LRT microbial targets does not indicate that the microorganism is the cause of the disease. Unyvero positive results do not rule out co-infection with microorganisms not detected by the Unyvero LRT Application. Negative results do not preclude lower respiratory infection, as the causative agent may be a microorganism not detected by this test.

A negative result for any antibiotic resistance marker does not indicate that detected microorganisms are susceptible to applicable antimicrobial agents. Detected resistance markers cannot be definitively linked to specific microorganisms, and may be present in organisms that are not detected by the Unyvero LRT Application such as organisms present as colonizing or normal flora.

Microbiology cultures of aspirates should be performed to obtain isolates for species identification and antimicrobial susceptibility testing, to differentiate quantities of identified microorganisms as well as normal flora present in the specimen and to identify potential microorganisms not targeted by

the Unyvero LRT Application.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Unyvero LRT Application, and substantially equivalent devices of this generic type, into Class II under the generic name “Device to detect and identify microorganisms and associated resistance marker nucleic acids directly in respiratory specimens”.

FDA identifies this generic type of device as: **Device to detect and identify microorganisms and associated resistance marker nucleic acids directly in respiratory specimens.**

A device to detect and identify microorganisms and associated resistance marker nucleic acids directly from respiratory specimens is an *in vitro* diagnostic device intended for the detection and identification of microorganisms and associated resistance markers in respiratory specimens collected from patients with signs or symptoms of respiratory infection. The device is intended to aid in the diagnosis of respiratory infection in conjunction with clinical signs and symptoms and other laboratory findings. These devices do not provide confirmation of antibiotic susceptibility since mechanisms of resistance may exist other than those detected by the device.

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 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 September 11, 2017, FDA received your De Novo requesting classification of the Unyvero LRT Application. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Unyvero LRT Application 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 FDA has determined that, for the previously stated indications for use, the Unyvero LRT Application 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 Risks to Health and Mitigation Measures

Identified Risks	Mitigation Measures
Incorrect identification or lack of identification of a pathogenic microorganism by the device can lead to improper patient management	General Controls and Special Controls (1), (2) (3), and (4)
Failure to correctly interpret test results	General Controls and Special Controls (1), (2)(iii), (2)(iv), (2)(v), (2)(vi), (2)(vii), (2)(viii), and (3)
Failure to correctly operate the instrument	General Controls and Special Controls (1), (2)(i), (4)(ii), (4)(iii) and (4)(iv)

In combination with the general controls of the FD&C Act, the device to detect and identify microorganisms and associated resistance marker nucleic acids directly in respiratory specimens is subject to the following special controls:

- (1) The intended use for the 21 CFR 809.10 labeling must include a detailed description of what the device detects, the type of results provided to the user, the clinical indications appropriate for test use, and the specific population(s) for which the device is intended.
- (2) The 21 CFR 809.10(b) labeling must include:
 - (i) A detailed device description, including all device components, control elements incorporated into the test procedure, instrument requirements, ancillary reagents required but not provided, and a detailed explanation of the methodology, including all pre-analytical methods for processing of specimens.
 - (ii) Performance characteristics from analytical studies, including but not limited to limit of detection, inclusivity, reproducibility, cross reactivity, interfering substances, competitive inhibition, carryover/cross contamination, specimen stability, and linearity, as applicable.
 - (iii) A limiting statement that the device is intended to be used in conjunction with clinical history, signs and symptoms, and results of other diagnostic tests, including culture and antimicrobial susceptibility testing.
 - (iv) A detailed explanation of the interpretation of test results for clinical specimens and acceptance criteria for any quality control testing.
 - (v) A limiting statement that negative results for microorganisms do not preclude the possibility of infection, and should not be used as the sole basis for diagnosis, treatment, or other patient management decisions.
 - (vi) If applicable, a limiting statement that detected microorganisms may not be the cause of lower respiratory tract infection and may be indicative of colonizing or normal respiratory flora.

- (vii) If applicable, a limiting statement that detection of resistance markers cannot be definitively linked to specific microorganisms and that the source of a detected resistance marker may be an organism not detected by the assay, including colonizing flora.
- (viii) If applicable, a limiting statement that detection of antibiotic resistance markers may not correlate with phenotypic gene expression.
- (3) The 21 CFR 809.10(b) labeling and any test report generated by the device must include a limiting statement that negative results for resistance markers do not indicate susceptibility of detected microorganisms.
- (4) Design verification and validation must include:
 - (i) Performance characteristics from clinical studies that include prospective (sequential) samples and, if appropriate, additional characterized samples. The study must be performed on a study population consistent with the intended use population and compare the device performance to results obtained from an FDA accepted reference method and/or FDA accepted comparator method, as appropriate. Results from the clinical studies must include the clinical study protocol (including predefined statistical analysis plan, if applicable), clinical study report, and results of all statistical analyses.
 - (ii) A detailed device description including the following:
 - (A) Thorough description of the assay methodology including, but not limited to, primer/probe sequences, primer/probe design, and rationale for target sequence selection, as applicable.
 - (B) Algorithm used to generate a final result from raw data (e.g., how raw signals are converted into a reported result).
 - (iii) A detailed description of device software, including, but not limited to, validation activities and outcomes.
 - (iv) As part of the risk management activities, an appropriate end user device training program must be offered as an effort to mitigate the risk of failure from user error.

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 device to detect and identify microorganisms and associated resistance marker nucleic acids directly in respiratory specimens 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); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); 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/MedicalDevices/DeviceRegulationandGuidance/>) and CDRH Learn (<http://www.fda.gov/Training/CDRHLearn>). 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 (<http://www.fda.gov/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 Kimberly Sconce at 301-796-6679.

Sincerely,

for

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