Centers for Disease Control and Prevention
Yon Yu, Pharm.D.
Associate Director for Regulatory Affairs
1600 Clifton Road NE, MS-C18
Atlanta, Georgia 30329

September 20, 2018

Re: K181205
Trade/Device Name: Non-variola Orthopoxvirus Real-time PCR Primer and Probe Set
Regulation Number: 21 CFR 866.3315
Regulation Name: Nucleic acid based reagents for detection of non-variola orthopoxviruses
Regulatory Class: Class II
Product Code: PBK
Dated: May 4, 2018
Received: May 7, 2018

Dear Yon Yu, Pharm.D.:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 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/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); 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 Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, 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).

Sincerely,

Uwe Scherf -S

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

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K181205

Device Name
Non-variola Orthopoxvirus Real-time PCR Primer and Probe Set

Indications for Use *(Describe)*
The Non-variola Orthopoxvirus Real-time PCR Primer and Probe Set is intended for the in vitro qualitative presumptive detection of non-variola Orthopoxvirus DNA extracted from human pustular or vesicular rash specimens and viral cell culture lysates submitted to a Laboratory Response Network (LRN) reference laboratory. The assay detects non-variola Orthopoxvirus DNA, including Vaccinia, Cowpox, Monkeypox and Ectromelia viruses at varying concentrations. This assay does not differentiate Vaccinia virus or Monkeypox virus from other Orthopoxviruses detected by this assay and does not detect Variola virus. Refer to the CDC algorithm, Acute, Generalized Vesicular or Pustular Rash Illness Testing Protocol in the United States for recommended testing and evaluation algorithms for patients presenting with acute, generalized pustular or vesicular rash illness.

Results of this assay are for the presumptive identification of non-variola Orthopoxvirus DNA. These results must be used in conjunction with other diagnostic assays and clinical observations to diagnose Orthopoxvirus infection. The assay should only be used to test specimens with low/moderate risk of smallpox. If a high risk of smallpox exists, viral culture should not be attempted. Negative results obtained with this device do not preclude Variola virus infection and should not be used as the sole basis for treatment or other patient management decisions.

Use is limited to Laboratory Response Network (LRN) designated laboratories.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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5. 510(k) Summary

This summary of 510(k) information is being submitted in accordance with the requirements of 21 CFR 807.92.

Assigned 510(k) number:	
Submitted by:	Centers for Disease Control and Prevention 1600 Clifton Road NE Atlanta, GA 30329
Contact Person:	CDR Yon Yu, Pharm.D. Associate Director for Regulatory Affairs Office of the Director National Center for Emerging and Zoonotic Infectious Diseases Centers for Disease Control and Prevention (Registration number: 1050190) 1600 Clifton Road, NE, MS C-18 Atlanta, GA 30329 (404) 639-3046 (office) (404) 639-1275 (fax) fkb8@cdc.gov
Date prepared:	May 4, 2018

Device trade name:	Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set
Classification name and regulation: (if applicable)	21 CFR 866.3316
Predicate device(s):	Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set (K053469)

Background

Variola virus, a member of the *Orthopoxvirus* genus, is the causative agent of smallpox and was certified eradicated in 1980 by the World Health Organization. At that time, smallpox vaccinations were ceased worldwide as a result. However, in recent years, concerns over the potential use of *Variola virus* as a biological weapon led the United States to resume smallpox vaccinations on a limited basis. Since the smallpox vaccine contains live *Vaccinia virus*, it is possible for vaccine recipients and/or their close contacts to develop adverse reactions to the vaccine including the emergence of pustules on the skin.

The Laboratory Response Network (LRN) is part of a national bioterrorism preparedness initiative created to ensure an effective laboratory response to biological threats by helping to improve the nation's public health laboratory infrastructure. Member laboratories must meet specific membership requirements and pass rigorous proficiency tests demonstrating their ability to accurately identify agents of concern. One of the major goals is the development and validation of rapid and specific assays for detection of biothreat agents and emerging infectious diseases. Accordingly, scientists at

the Centers for Disease Control and Prevention have developed several real-time PCR based assays to detect non-variola *Orthopoxvirus* and other potential biothreat agents in an effort to meet the need for rapid detection.

The Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set was developed for use in conjunction with clinical observations and other tests as described in the CDC algorithm, Acute, Generalized Vesicular or Pustular Rash Illness Testing Protocol in the United States. The assay is designed to aid in the identification of the causative agent of a pustular or vesicular rash illness and to help rule out the presence of *Variola virus* in patients presenting with pustular rash illness.

This assay detects most commonly known human pathogenic *Orthopoxviruses* (e.g. *Vaccinia*, *Cowpox*, and *Monkeypox viruses*) but does not detect *Variola virus*, the causative agent of smallpox. *Vaccinia virus* infection in the United States usually occurs in conjunction with smallpox vaccination or contact with a smallpox vaccine recipient. *Monkeypox* and *Cowpox viruses* are endemic to locations outside the United States, with the exception of the 2003 monkeypox outbreak associated with prairie dogs, which became infected due to imported African rodents.

Device Description

With the exception of some reagents, the Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set device description remains unchanged from the original submission (K053469).

The Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set Assay uses a fluorogenic probe, consisting of an oligonucleotide with a reporter dye (FAM) attached to the 5' end and a quencher dye (BHQ1) attached at or near the 3' end. The probe anneals to a specific target sequence located between the forward and reverse primers. During the extension phase of the PCR cycle, the 5' nuclease activity of the *Taq* polymerase degrades the probe causing the reporter dye to separate from the quencher dye, thereby generating a fluorescent signal. With each cycle, additional reporter dye molecules are cleaved from their respective probes and the fluorescence intensity is monitored during the PCR in real-time. The *Taq* polymerase used in this assay is inactive at room temperature and is activated by incubation at 95°C, thus minimizing the production of nonspecific amplification products.

Each extracted DNA sample is tested using the Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe set along with an internal control primer and probe set(s) to demonstrate adequate DNA extraction and isolation, proper function of common reagents and equipment, and the absence of inhibitory substances.

Intended Use

The Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set is intended for the *in vitro* qualitative presumptive detection of non-variola *Orthopoxvirus* DNA extracted from human pustular or vesicular rash specimens and viral cell culture lysates submitted to a Laboratory Response Network (LRN) reference laboratory. The assay detects non-variola *Orthopoxvirus* DNA, including *Vaccinia, Cowpox, Monkeypox* and *Ectromelia*

viruses at varying concentrations. This assay does not differentiate *Vaccinia virus* or *Monkeypox virus* from other *Orthopoxviruses* detected by this assay and does not detect *Variola virus*. Refer to the CDC algorithm, Acute, Generalized Vesicular or Pustular Rash Illness Testing Protocol in the United States for recommended testing and evaluation algorithms for patients presenting with acute, generalized pustular or vesicular rash illness.

Results of this assay are for the presumptive identification of non-variola *Orthopoxvirus* DNA. These results must be used in conjunction with other diagnostic assays and clinical observations to diagnose *Orthopoxvirus* infection. The assay should only be used to test specimens with low/moderate risk of smallpox. If a high risk of smallpox exists, viral culture should **not** be attempted. Negative results obtained with this device do not preclude *Variola virus* infection and should not be used as the sole basis for treatment or other patient management decisions.

Use is limited to Laboratory Response Network (LRN) designated laboratories.

Device Comparison

The following table summarizes the similarities and differences between the cleared assay and the new submission for this device.

	New Submission	Original Submission
Device	Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set	Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set (K053469)
Intended Use	The Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set is intended for the *in vitro* qualitative presumptive detection of non-variola *Orthopoxvirus* DNA extracted from human pustular or vesicular rash specimens and viral cell culture lysates submitted to a Laboratory Response Network (LRN) reference laboratory. The assay detects non-variola *Orthopoxvirus* DNA, including *Vaccinia, Cowpox, Monkeypox* and *Ectromelia viruses* at varying concentrations. This assay does not differentiate *Vaccinia virus* or *Monkeypox virus* from other *Orthopoxviruses* detected	The Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set is intended for the *in vitro* qualitative presumptive detection of non-variola *Orthopoxvirus* DNA extracted from human pustular or vesicular rash specimens and viral cell culture lysates submitted to a Laboratory Response Network (LRN) reference laboratory. The assay detects non-variola *Orthopoxvirus* DNA, including *vaccinia, cowpox, monkeypox* and *ectromelia viruses* at varying concentrations. This assay does not differentiate *vaccinia virus* or *monkeypox virus* from other orthopoxviruses

	by this assay and does not detect *Variola virus*. Refer to the CDC algorithm, Acute, Generalized Vesicular or Pustular Rash Illness Testing Protocol in the United States for recommended testing and evaluation algorithms for patients presenting with acute, generalized pustular or vesicular rash illness. Results of this assay are for the presumptive identification of non-variola *Orthopoxvirus* DNA. These results must be used in conjunction with other diagnostic assays and clinical observations to diagnose Orthopoxvirus infection. The assay should only be used to test specimens with low/moderate risk of smallpox. If a high risk of smallpox exists, viral culture should **not** be attempted. Negative results obtained with this device do not preclude *Variola virus* infection and should not be used as the sole basis for treatment or other patient management decisions. **Use is limited to Laboratory Response Network (LRN) designated laboratories.**	detected by this assay and does not detect *variola virus*. Refer to the CDC algorithm, Acute, Generalized Vesicular or Pustular Rash Illness Testing Protocol in the United States for recommended testing and evaluation algorithms for patients presenting with acute, generalized pustular or vesicular rash illness. This assay should be used in conjunction with other diagnostic assays and clinical observations for the following indications: (1) to serve as an aid in determining whether *Vaccinia virus* is the causative agent of a vaccination adverse event in recipients of the smallpox vaccine (which uses live *Vaccinia virus*) (2) to serve as an aid in determining *Vaccinia virus* infection in smallpox vaccine contacts presenting with unclear etiology and pustules resembling *Vaccinia virus* infection (3) to determine infection with *vaccinia* or other non-variola orthopoxviruses in individuals presenting with pustular or vesicular rash illness (4) to aid in the differential diagnosis of smallpox (5) to aid in the identification of viral cell cultures from patients with low/moderate risk of smallpox

		NOTE: If a high risk of smallpox exists, viral culture should **not** be attempted. **Use is limited to Laboratory Response Network (LRN) designated laboratories.**
Principle of Operation	Unchanged	Nucleic acid amplification and fluorescent probe detection
Sample Types	Unchanged	• Vesicle fluid, skin, crust, "roof" • Dry or wet swab of lesion (dry swab is preferred) • Touch prep (slide) of lesion • Fresh biopsy of pustule or vesicle (no formalin) • Viral cell culture lysates
Instrumentation and Software	Unchanged	Real-time PCR instrumentation and software

Establishment of Performance Characteristics

Inquiries regarding performance characteristics for the Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set should be directed to the Centers for Disease Control and Prevention.

Analytical Limit of Detection (LoD)

The limit of detection for the Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set was determined through an analytical sensitivity study.

Analytical Sensitivity and Specificity

Inquiries regarding performance characteristics for the Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set should be directed to the Centers for Disease Control and Prevention.

Clinical Performance

Inquiries regarding clinical performance characteristics for the Non-variola *Orthopoxvirus* Real-time PCR Primer and Probe Set should be directed to the Centers for Disease Control and Prevention.