DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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LUMINEX CORPORATION October 5, 2015
RONALD DUNN
SENIOR DIRECTOR GLOBAL REGULATORY AFFAIRS
12212 TECHNOLOGY BLVD.
AUSTIN TX 78727

Re: K151906
Trade/Device Name: ARIES® HSV 1&2 Assay
Regulation Number: 21 CFR 886.3309
Regulation Name: Herpes virus nucleic acid-based cutaneous and mucocutaneous lesion panel
Regulatory Class: II
Product Code: PGI, OOI
Dated: July 10, 2015
Received: July 13, 2015

Dear Mr. Dunn:

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. 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 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 Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. 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 the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Stephen J. Lovell -S for

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: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K151906

Device Name
ARIES® HSV 1&2 Assay

Indications for Use *(Describe)*
The ARIES® HSV 1&2 Assay is a real-time polymerase chain reaction (PCR) based qualitative in vitro diagnostic test for the direct detection and differentiation of Herpes Simplex Virus 1 and 2 (HSV 1 and HSV 2) DNA in cutaneous or mucocutaneous lesion specimens from symptomatic patients. The test is indicated for use as an aid in diagnosis of HSV infection in symptomatic patients. The ARIES® HSV 1&2 Assay is indicated for use on the ARIES® System.

WARNING: The ARIES® HSV 1&2 Assay is not FDA cleared for use with cerebrospinal fluid (CSF). The assay is not intended to be used for prenatal screening.

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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510(k) Summary

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

510(k) Number:
K151906

Submission Type:
Traditional 510(k), New Device

Measurand:
Target DNA sequences from Herpes Simplex Virus type 1 (HSV-1) and Herpes Simplex Virus type 2 (HSV-2)

Type of Test:
Qualitative nucleic acid multiplex test

Applicant:
Luminex Corporation
12212 Technology Blvd
Suite 130
Austin, TX 78727

Proprietary and Established Names:
ARIES® HSV 1&2 Assay

Regulatory Information:

Regulatory Information

Product Code	Classification	Regulation Section	Review Panel
PGI	II	21 CFR 866.3309– Herpes simplex virus nucleic acid amplification assay	Microbiology (83)
OOI	II	21 CFR 862.2570 Multiplex Instrument System	Chemistry (75)

Device Components:

Device Components

Product	Description
ARIES® HSV 1&2 Assay Cassette Kit	24 ARIES® HSV 1&2 Assay cassettes which contain the necessary reagents for sample extraction, nucleic acid purification and amplification.
ARIES® HSV1&2 Assay Protocol File Kit	A USB thumb drive containing the ARIES® HSV 1&2 Assay Protocol File, ARIES® HSV 1&2 Assay Protocol File package insert and ARIES® System Quick Guide.
ARIES® System	An *in vitro* diagnostic (IVD) platform that performs nucleic acid based tests in clinical laboratories. The Luminex ARIES® System is capable of automated extraction and purification of nucleic acids from multiple sample types as well as the automated amplification and detection of target nucleic acid sequences by fluorescence-based PCR.

Intended Use:

The ARIES® HSV 1&2 Assay is a real-time polymerase chain reaction (PCR) based qualitative in vitro diagnostic test for the direct detection and differentiation of Herpes Simplex Virus 1 and 2 (HSV 1 and HSV 2) DNA in cutaneous or mucocutaneous lesion specimens from symptomatic patients. The test is indicated for use as an aid in diagnosis of HSV infection in symptomatic patients. The ARIES® HSV 1&2 Assay is indicated for use on the ARIES® System

WARNING: The ARIES® HSV 1&2 Assay is not FDA cleared for use with cerebrospinal fluid (CSF). The assay is not intended to be used for prenatal screening.

Indication(s) for use: Same as intended use.

Special instrument requirements: ARIES® System

Device Description:

The Luminex ARIES® HSV 1 & 2 Kit is a polymerase chain reaction (PCR)-based qualitative in vitro diagnostic test for the direct detection and differentiation of herpes simplex virus (HSV) DNA using cutaneous and mucocutaneous lesion swab specimens. Patient lesion swab specimens are

collected in Copan Universal Transport Medium, or identical Copan manufactured media formulations (Becton Dickinson Universal Viral Transport Media, Copan branded Universal Transport Medium for LabCorp, and the Quest Viral Culture Media) and transported to the laboratory. The specimen is pipetted into a cassette specific to the ARIES® HSV 1&2 Assay. In the cassette the specimen is lysed and nucleic acid is extracted using the ARIES® System and an extraction/ PCR cassette specific to the ARIES® HSV 1&2 Kit. An extractable sample processing control (SPC) target is present in the ARIES® HSV 1&2 assay cassette and is processed with the specimen. The Ct value of the SPC is designed to verify proper specimen lysis and nucleic acid extraction, to identify PCR inhibition, if any, and verify proper function of the extraction system and real-time instrument. The Tm value of the SPC is used as a reference for determining the target Tm.

The extracted nucleic acid is transferred via magnetic beads to the ARIES® HSV 1 & 2 Kit lyophilized PCR reagents in the cassette that contain a primer pair specific to HSV 1 and HSV 2 and a primer pair specific to the SPC sequence. The specific primer pairs are labeled with distinct fluorophore labels. PCR amplification is performed and assay fluorescence is monitored on the Luminex ARIES® System. Incorporation of the quencher-labeled nucleotide causes a decrease in assay fluorescence. Following amplification, the reaction is slowly heated and fluorescence is monitored. The strands of the amplification products will separate at a specific melting temperature (Tm) that is determined by an increase in fluorescence as the strands are separated. The sequences between the PCR primer binding sites of the HSV 1 and HSV 2 amplicons have different base compositions that are distinguished by their different Tm. The instrument fluorescence output is analyzed and test results are determined using the ARIES® HSV 1 & 2 Kit assay protocol file. A printed results report is generated.

The Luminex ARIES® HSV 1&2 Assay chemistry is based on an expanded genetic alphabet technology, consisting of synthetic DNA base pair 2'-deoxy-5-methyl-isocytidine (iC): 2'-deoxyisoguanosine (iG). The isobases (iC and iG) pair specifically with each other and not with natural nucleotides. In addition isobases are efficiently incorporated during PCR. During PCR amplification, a quencher-modified iGTP is incorporated by the polymerase opposite an iC and a fluorophore reporter attached to a PCR primer. If the target is present and is amplified, assay fluorescence decreases with every cycle as amplification product accumulates. The decrease in assay fluorescence is monitored in real time using the Luminex ARIES® Instrument. Following PCR, the amplification products are thermally denatured and assay fluorescence is monitored. The strands of the amplification products are separated and assay fluorescence increases, thus enabling determination of the melting temperature (Tm) of the amplicon.

Substantial Equivalence Information:

a. Predicate device name(s):
illumi*gene*® HSV 1&2 DNA Amplification Assay (Meridian Bioscience, Inc.)

b. Predicate 510(k) number(s):
K151046

c. Comparison to Predicate:

The following tables compare ARIES® HSV 1&2 Assay to ***illumi****gene*® HSV 1&2 DNA Amplification Assay (K151046). The similarities and differences between the new device and the predicate are outlined in the tables below.

Similarities between New Device and Predicate

Similarities		
Device Characteristic	**ARIES® HSV 1 & 2 Assay (New Device)**	***illumigene*® HSV 1&2 DNA Amplification Assay (Predicate Device - K151046)**
Intended use	The ARIES® HSV 1&2 Assay is a real-time polymerase chain reaction (PCR) based qualitative *in vitro* diagnostic test for the direct detection and differentiation of Herpes Simplex Virus 1 and 2 (HSV 1 and HSV 2) DNA in cutaneous or mucocutaneous lesion specimens from symptomatic patients. The test is indicated for use as an aid in diagnosis of HSV infection in symptomatic patients. The ARIES® HSV 1&2 Assay is indicated for use on the ARIES® System. ***Warning:*** The ARIES® HSV 1&2 Assay is not FDA cleared for use with cerebrospinal fluid (CSF). The assay is not intended to be used for prenatal screening.	The ***illumi****gene* HSV 1&2 DNA amplification assay, performed on the ***illumi****pro-10™*, is a qualitative in vitro diagnostic test for the direct detection and differentiation of herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) DNA in cutaneous and mucocutaneous lesion specimens from male and female patients suspected of Herpetic infections. ***illumi****gene* HSV 1&2 utilizes loop-mediated isothermal DNA amplification (LAMP) technology to detect HSV-1 and HSV-2 by targeting segments of the herpes simplex virus 1 and herpes simplex virus 2 genomes. Results from ***illumi****gene* HSV 1&2 are used as an aid in the diagnosis of HSV infection in symptomatic patients. The assay is intended for use in hospital, reference or state laboratory settings. This device is not intended for nonlaboratory point-of-care use. ***Warning: illumi****gene* HSV 1&2 is not FDA cleared for use with cerebrospinal fluid (CSF) or to aid in the diagnosis of HSV infections of the central nervous system (CNS). The device is not intended for prenatal screening.
Specimen Types	Male and female cutaneous and mucocutaneous lesion swab specimens	Male and female cutaneous and mucocutaneous lesion swab specimens
Test Principle	DNA amplification	DNA amplification
Assay Results	Qualitative detection and differentiation of HSV-1 and HSV-2 DNA	Qualitative detection and differentiation of HSV-1 and HSV-2 DNA

Differences between New Device and Predicate

Differences		
Device Characteristic	**ARIES® HSV 1 & 2 Assay (New Device)**	***illumigene*® HSV 1&2 DNA Amplification Assay (Predicate Device - K151046)**
Sample extraction and Amplification Instrumentation	Automated sample extraction; Real-time PCR amplification/detection using the Luminex ARIES® System	Manual sample preparation; isothermal Loop Mediated Amplification (LAMP) using the ***illumi****pro-10*™.
Detection Method	Pairs fluorescent-labeled primers with quencher labeled nucleotides. Measures decrease in assay fluorescence with each PCR cycle.	Visible Light Transmission (Turbidity).

Analytical Performance:

Limit of Detection

A Limit of Detection (LoD) study was performed to evaluate the analytical sensitivity of the ARIES® HSV 1&2 Assay using two representative reference strains of HSV-1 (MacIntyre and F) and two representative strains of HSV-2 (MS & G). Preliminary LoD concentrations were determined by performing a six point, five-fold dilution series, in Copan Universal Transport Media, of each quantified ($TCID_{50}$/mL) strain. The observed LoD of a HSV strain was determined as the lowest concentration that had a positivity rate of ≥ 95%.

The LoD concentrations determined in the preliminary study were confirmed with the same HSV-1 and HSV-2 reference strains diluted to the preliminary LoD concentrations and tested with twenty-four (24) replicates. The final LoD concentrations are presented in the table below.

Limit of Detection of the ARIES® HSV 1&2 Assay

HSV Type	Strain	LoD Concentration ($TCID_{50}$/mL)	Positivity
HSV-1	**MacIntyre**	7.11E+03	24/24 (100%)
	F	16.5	23/24 (95.8%)
HSV-2	**MS**	2.7	24/24 (100%)
	G	2.8	24/24 (100%)

Assay LoD: The final assay LoD claim is 7.11E+03 $TCID_{50}$/mL for HSV-1 and 2.7 $TCID_{50}$/mL for HSV-2.

Co-infection Verification

A study was designed to evaluate the ability of the ARIES® HSV 1&2 Assay to detect HSV-1 and HSV-2 analytes when both are present in one specimen. Analytes were tested at high (200X LoD) and low concentrations (5X LoD) using 12 replicates. The ARIES® HSV 1&2 Assay may not detect a co-infection of HSV-1 and HSV-2 in cases where the two virus types are not equally represented in clinical specimens Co-infections were only detected when both analytes were present at equal concentrations. An HSV analyte at 5X LoD was not detected in the presence of a different HSV analyte at 200X LoD. Results are presented in the table below.

Co-Infection Results

Condition	Result	Percent of Replicates
HSV-1 High / HSV-2 Low	HSV 1 Positive	100% (12/12)
HSV-2 High / HSV-1 Low	HSV 2 Positive	100% (12/12)
HSV-1 High/HSV-2 High	HSV 1&2 Positive	100% (12/12)

Interfering Substances

The effect of potential interfering substances on the ARIES® HSV 1&2 Assay was evaluated by testing five replicates of each HSV 1, HSV 2 near the device's Limit of Detection (LoD), and negative samples (Copan UTM) spiked with 28 potential interfering substances. At the tested concentrations of the substances, the substances do not interfere with the assay. All HSV positive results were 100% positive and all HSV 1&2 negative results were 100% negative. Results are presented below.

Interfering Substance Panel

Interfering Substance	Test Concentration
Abreva (Docosanol)	10%
Acyclovir (Acycloguanosine)	2.5 mg/mL
Buffy Coat	5%
Carmex Cold Sore Lip Balm	1%
Casein	7.0 mg/mL
Clotrimazole 3 Vaginal Cream	1%
Toothpaste	5%
Anti-itch cream (Benzalkonium Chloride)	5%
Cidofovir	2.5 mg/mL
Douche	10%
Foscarnet	2.5 mg/mL
Ganciclovir	2.5 mg/mL
Valganciclovir	2.5 mg/mL
Leukocytes	10%
Interfering Substance	**Test Concentration**

Lip Clear Lysine+	1%
Listerine	10%
Male Urine	10%
Female Urine	10%
Whole Blood	10%
Monistat 1	5%
Monistat 3	5%
Albumin	10 mg/mL
Releev Cold Sore Treatment	1%
K-Y Brand Jelly	5%
Spermicide	5%
Tioconazole	5%
Vagisil Cream	1%
YeastGard	1%

Analytical Specificity

A study was performed to evaluate cross reactivity and interference of the ARIES® HSV 1&2 Assay with 61 microorganisms that might be found in cutaneous and mucocutaneous lesion specimens. The effect of potential cross reactivity or interference was evaluated by testing five replicates of each HSV 1, HSV 2 near the device's Limit of Detection (LoD), and Negative replicates (Copan UTM) spiked with 61 potential cross reacting organisms. Bacteria were tested at 10^6 cfu/ml or higher for bacteria and 105 pfu/ml or higher for viruses. At the tested concentrations of the organisms, the organisms do not cross react or interfere with the assay: all HSV positive results were 100% positive and all HSV 1&2 Negative results were 100%. Results are presented below.

Cross-Reacting and Microbial Interference Panel

Microorganism	Test Concentration
Acinetobacter calcoaceticus	9.27×10^7 cfu/mL
Bacteroides fragilis	4.2×10^8 cfu/mL
Candida albicans	1.74×10^7 cfu/mL
Candida glabrata	7.87×10^6 cfu/mL
Chlamydia trachomatis	1.8×10^4 $TCID_{50}$/mL
Clostridium sordellii	4.9×10^6 cfu/mL
Cytomegalovirus (AD169 Strain)	1.15×10^6 $TCID_{50}$/mL
Enterobacter cloacae	7.43×10^8 cfu/mL
Enterococcus faecalis	4.57×10^8 cfu/mL
Enterovirus (Type 71)	4.17×10^4 $TCID_{50}$/mL
Epstein-Barr virus (B95-8 Strain)	9.27×10^7 copy/mL
Microorganism	**Test Concentration**

Escherichia coli	5.13×10^8 cfu/mL
Gardnerella vaginalis	5.43×10^6 cfu/mL
Hepatitis A Virus	8.47×10^2 IU/mL
Hepatitis B Virus	5.62×10^8 IU/mL
HIV-1	1.05×10^5 $TCID_{50}$/mL
Human Herpes 6 virus (Z29 Strain)	4.17×10^4 $TCID_{50}$/mL
Human Herpes 7 virus (SB Strain)	1.15×10^6 $TCID_{50}$/mL
Human Papilloma virus	1.68×10^9 copy/mL
Lactobacillus acidophilus	2.00×10^7 cfu/mL
Legionella micdadei	2.70×10^8 cfu/mL
Mobiluncus mulieris	3.18×10^8 cfu/mL
Moraxella cartarrhalis	9.90×10^5 cfu/mL
Mycoplasma hominis	3.6×10^6 cfu/mL
Mycoplasma orale	1.4×10^8 cfu/mL
Mycoplasma salivarium	4.7×10^6 cfu/mL
Neisseria gonorrhoeae	5.73×10^7 cfu/mL
Propionibacterium acnes	3.7×10^8 cfu/mL
Proteus mirabilis	2.10×10^8 cfu /mL
Rubella virus	1.26×10^5 $TCID_{50}$/mL
Salmonella enteritidis	2.08×10^7 cfu/mL
Serratia marcescens	4.07×10^8 cfu/mL
Staphylococcus aureus	1.42×10^9 cfu/mL
Staphylococcus epidermidis	3.47×10^8 cfu/mL
Streptococcus pyogenes	2.60×10^8 cfu/mL
Staphylococcus saprophyticus	6.60×10^6 cfu/mL
Streptococcus agalactiae	8.67×10^7 cfu/mL
Toxoplasma gondii	6.6×10^5 tachyzoites/mL
Treponema pallidum	9.8×10^6 genome copy/mL
Trichomonas vaginalis	4.21×10^5 trophozoites/mL

Microorganism	Test Concentration
Varicella Zoster virus	2.45×10^4 $TCID_{50}$/mL
Acinetobacter Iwoffi	8.27×10^7 cfu/mL
Haemophilus influenza type B	5.33×10^7 cfu/mL
Klebsiella pneumoniae	6.28×10^8 cfu/mL
Neisseria meningitides Serogroup A	7.07×10^8 cfu/mL
Prevotella melaninogenica	4.10×10^6 cfu/mL
Streptococcus mitis	5.73×10^7 cfu/mL
Streptococcus mutans	4.37×10^8 cfu/mL
Streptococcus pneumoniae	9.2×10^7 cfu/mL
Streptococcus salivarius	7.47×10^7 cfu/mL
Candida parapsilosis	2.87×10^6 cfu/mL
Candida tropicalis	2.15×10^6 cfu/mL
Human genomic DNA	10 µg/mL
Adenovirus 2	5.01×10^5 U/mL
Candida guilliermondii Z008	1.78×10^7 cfu/mL
Candida krusei Z009	6.3×10^6 cfu/mL
Candida lusitaniae Z010	1.42×10^8 cfu/mL
Fusobacterium nucleatum	N/A[a]
Haemophilus ducreyi	2.05×10^6 cfu/mL
Mobiluncus curtisii V125 [DSM 2711] ATCC 43063	$>10^3$ cfu/mL
Simian Virus type 40 Pa-57 ATCC strain VR-239	2.8×10^6 $TCID_{50}$/mL

[a] Concentration information not available.

Reproducibility

Reproducibility of the ARIES® HSV 1&2 Assay was evaluated by testing one lot of ARIES® HSV 1&2 Assay Cassettes on two ARIES® instruments by two operators at each of three sites on five non-consecutive days. A reproducibility panel was prepared containing a moderate positive (approximately 4X LoD for both HSV 1 and HSV 2), low positive (approximately 1X LoD for both HSV 1 and HSV 2) and high negative (approximately 0.1X LoD for HSV 1 and 0.4X LoD for HSV 2) independently for HSV 1 and HSV 2 as well as a negative. The reproducibility panels were created by an independent operator and blinded. The results of the reproducibility study are presented in the table below.

Reproducibility Panel Results

	Site 1				Site 2				Site 3				Total Agreement with expected results	95% Confidence Interval
	Agreement with expected results[a]	Avg T_m	% CV T_m	Avg T_m Deflection[b]	Agreement with expected results[a]	Avg T_m	% CV T_m	Avg T_m Deflection[b]	Agreement with expected results[a]	Avg T_m	% CV T_m	Avg T_m Deflection[b]		
HSV-1 Moderate Positive	30/30	85.5	0.16%	2.25E+06	30/30	85.5	0.12%	2.56E+06	30/30	85.6	0.18%	2.72E+06	90/90 (100%)	96.0-100%
HSV-1 Low Positive	30/30	85.5	0.16%	2.04E+06	30/30	85.6	0.16%	2.24E+06	30/30	85.5	0.16%	2.45E+06	90/90 (100%)	96.0-100%
HSV-1 High Negative	11/30	85.4	0.17%	1.39E+06	9/30	85.5	0.20%	2.33E+06	9/30	85.5	0.17%	2.06E+06	29/90 (32.2%)	22.8-42.9%
HSV-2 Moderate Positive	30/30	87.9	0.17%	2.17E+06	30/30	87.8	0.16%	2.52E+06	30/30	87.8	0.15%	2.43E+06	90/90 (100%)	96.0-100%
HSV-2 Low Positive	30/30	87.8	0.11%	1.95E+06	29/30	87.7	0.17%	2.23E+06	30/31	87.7	0.16%	2.04E+06	89/91 (97.8%)	92.3-99.7%
HSV-2 High Negative	30/30	87.7	0.19%	1.75E+06	30/30	87.7	0.14%	1.98E+06	23/30	87.7	0.15%	1.94E+06	83/90 (92.2%)	84.6-96.8%
HSV1&2 Negative	30/30	76.4	0.30%	2.76E+05	30/30	76.3	0.24%	3.11E+05	30/30	76.3	0.68%	3.34E+05	90/90 (100%)	96.0-100%

[a] Agreement with expected results for the HSV 1&2 negative reflects SPC positivity since no HSV 1 or HSV 2 was detected. Expected result for HSV 1 Moderate Positive target was 100% HSV 1 Positive, HSV 1 Low Positive was approximately 95% HSV 1 Positive, HSV 1 High Negative was 20% to 80% HSV 1 Positive, HSV 2 Moderate Positive target was 100% HSV 2 Positive, HSV 2 Low Positive was approxi- mately 95% HSV 2 Positive, HSV 2 High Negative was 20% to 80% HSV 2 Positive, and HSV 1&2 Negative was 100% HSV 1&2 Negative.

[b] Average T_m deflection (RFU) was calculated using all of the positive replicates for that target type. Average T_m deflection for the HSV 1&2 Negative reflects SPC T_m deflection since no HSV 1 or HSV 2 was detected.

Precision

Within Laboratory Precision/Repeatability of the ARIES® HSV 1&2 Assay was evaluated by two operators performing testing across multiple ARIES® instruments using one lot of ARIES® HSV 1&2 Assay Cassettes. Testing was performed in 10 days and included a total of 216 replicates used in assessing repeatability. A reproducibility panel was prepared containing moderate positive (approximately 4X LoD for both HSV 1 and HSV 2), low positive (approximately 1X LoD for both HSV 1 and HSV 2) and high negative (approximately 0.1X LoD for HSV 1 and 0.4X LoD for HSV 2) samples independently for HSV 1 and HSV 2 as well as a negative sample. The results of the repeatability study are shown in the table below.

Repeatability Panel Results[a]

Target Type	Agreement with Expected Results[b]	95% Confidence Interval	Average T_m	% Coefficient of Variation - T_m	Average T_m Deflection[c]
HSV 1 Moderate Positive	100% (72/72)	95.0 – 100%	85.6	0.17%	3.28E+06
HSV 1 Low Positive	100% (72/72)	95.0 – 100%	85.6	0.13%	2.88E+06
HSV 1 High Negative	45.80% (33/72)	34.0 – 58.0%	85.4	0.12%	2.18E+06
HSV 2 Moderate Positive	100% (72/72)	95.0 – 100%	87.9	0.16%	3.16E+06
HSV 2 Low Positive	100% (72/72)	95.0 – 100%	87.8	0.15%	2.75E+06
HSV 2 High Negative	97.40% (76/78)	91.0 – 99.7%	87.8	0.17%	2.39E+06
HSV 1&2 Negative	100% (72/72)	95.0 – 100%	76.5	0.66%	4.41E+05

[a] An overall invalid rate of 0.8% (4/514) was observed.

[b] Expected result for HSV 1 Moderate Positive target was 100% HSV 1 Positive, HSV 1 Low Positive was approximately 95% HSV 1 Positive, HSV 1 High Negative was 20% to 80% HSV 1 Positive, HSV 2 Moderate Positive target was 100% HSV 2 Positive, HSV 2 Low Positive was approximately 95% HSV 1 Positive, HSV 2 High Negative was 20% to 80% Positive, and HSV 1&2 Negative was 100% HSV 1&2 Negative.

[c] Average T_m deflection (RFU) was calculated using all of the positive replicates for that target type. Average T_m deflection for the HSV 1&2 Negative reflects SPC T_m deflection since no HSV 1 or HSV 2 was detected.

Carryover/Cross-Contamination

Carry-over and cross contamination for the ARIES® HSV 1&2 Assay was assessed by testing fifteen (15) high positive HSV 1 samples, 15 high positive HSV 2 samples and thirty (30) HSV negative

samples (Copan UTM). Samples were tested in an alternating pattern with high positive samples run adjacent to negative samples across ten (10) consecutive runs. No carry-over and cross contamination was observed. The overall percent agreement was 100% for positive and negative samples.

Fresh and Frozen Specimen Stability

The objective of fresh specimen stability testing was to evaluate the stability of specimens when stored at 2 – 8°C. This was assessed by testing 6 replicates of each contrived target concentration across 6 different time points. The concentrations tested were a moderate positive, low positive and high negative for HSV 1 and HSV 2 as well as a negative concentration. Moderate positive specimens gave the expected result of 100% positivity, low positive specimens gave the expected result of approximately 95% positivity and high negative specimens gave the expected result of 20 – 80% positivity. Finally negative specimens gave the expected result of 0% positivity. The data from this stability study support the claim in the package insert that fresh specimens for the ARIES® HSV 1&2 Assay can be held at 2 – 8°C for up to 15 days.

The objective of frozen specimen stability was to evaluate the stability of specimens when stored at -65 to -95°C. This was assessed by testing 6 replicates of each of contrived target concentrations in Copan across 7 different time points extending out to 12 months. The concentrations used for testing are a moderate positive, low positive and high negative concentration for HSV 1 and HSV 2 as well as a negative concentration. Data up to 3 months has been collected with all targets yielding the expected result. Moderate positive specimens are 100% positive, low positive specimens are positive approximately 95% of the time, high negative specimens are positive 20 – 80% of the time and negative specimens are negative 100% of the time. HSV 1&2 specimens are stable for up to 3 months when stored at -65 to -95°C.

Reagent Stability

The objective of ARIES® HSV 1&2 Assay Cassette real time stability testing was to evaluate the stability of ARIES® HSV 1&2 Assay Cassette in order to establish a shelf life. This was assessed by testing 4 replicates of HSV 1, 4 replicates of HSV 2 and 4 replicates of negative (Copan UTM) targets on three different lots of ARIES® HSV 1&2 Assay Cassettes stored at 2 different temperatures (2 – 8°C and 25°C) at 10 different time points extending out to 19 months. Data up to 3 months has been collected and to date all targets for all lots and all storage temperatures have given the expected result. HSV 1 replicates are 100% HSV 1 Positive, HSV 2 replicates are 100% HSV 2 Positive and negative replicates are 100% HSV 1&2 Negative. Therefore, ARIES® HSV 1&2 Assay Cassettes are stable for 3 months when stored at both 4°C and Room Temperature (25°C).

Clinical Performance:

The performance of ARIES® HSV 1&2 Assay was assessed at three (3) geographically diverse clinical sites in the United States. A total of 1963 left-over clinical specimens from symptomatic male and female patients were included in the clinical study. Of these, 1500 specimens were prospectively collected (all comers). The remaining 463 were pre-selected for cutaneous and mucocutaneous lesion types that were under-represented in the initial prospective sample set. All of the pre-selected specimens were also prospectively collected. Of the 1963 specimens tested, fifty five (55) specimens were lesion sources from anatomical sites that could not be determined, four (4) specimens remained invalid upon re-testing by ARIES® HSV 1&2 Assay and three (3) were unavailable for re-testing. All of these 62 specimens were excluded from accuracy determinations.

The reference/comparative method used to evaluate the clinical performance of ARIES® HSV 1&2 Assay was the ELVIS® HSV ID and D^3 Typing Test System. Because the ELVIS® method provides no information on HSV-1 patient infected status (positive or negative) in specimens that test positive for HSV-2, all specimens that were positive for HSV-2 by the ELVIS® HSV-ID and D^3 Typing System were excluded from the analysis of HSV-1 clinical performance.

The performance of ARIES® HSV 1&2 assay when compared to ELVIS® viral culture is summarized for cutaneous and mucocutaneous lesions in the tables below:

Summary of HSV 1 Results for Cutaneous Lesions (N=347)

ARIES® HSV 1&2 Assay	Reference Method		
	Positive	**Negative**	**Total**
Positive	51	17[1]	68
Negative	5[2]	274	279
TOTAL	56	291	347
		95% CI	
Sensitivity	91.1% (51/56)	80.4% - 97.0%	
Specificity	94.2% (274/291)	90.8% - 96.6%	

[1] Thirteen (13) HSV-1 ARIES® positive specimens that were negative by the reference method were positive by bi-directional sequencing analysis using analytically validated primers that targeted genomic regions distinct from the ARIES® HSV 1&2 Assay. The remaining four (4) false positive specimens were negative for both HSV 1 and HSV 2 by bi- directional sequencing.

[2] All five (5) HSV-1 ARIES® negative specimens that were positive by the reference method were negative by bi-directional sequencing analysis using analytically validated primers that targeted genomic regions distinct from the ARIES® HSV 1&2 Assay. One of these specimens was positive for HSV-2 by both ARIES® and sequencing

Summary of HSV 1 Results for Mucocutaneous Lesions (N=1190)

ARIES® HSV 1&2 Assay	Reference Method		
	Positive	**Negative**	**Total**
Positive	262	42[1]	304
Negative	8[2]	878	886
TOTAL	270	920	1190
		95% CI	
Sensitivity	97.0% (262/270)	94.2% - 98.7%	
Specificity	95.4% (878/920)	93.9% - 96.7%	

[1] Nineteen (19) HSV 1 ARIES® positive specimens that were negative by the reference method were positive by bi-directional sequencing analysis using analytically validated primers that targeted genomic regions distinct from the ARIES® HSV 1&2 Assay. Twenty (20) false positive specimens were negative for both HSV-1 and HSV-2 by bi-directional sequencing. The remaining three (3) specimens were unavailable (QNS) for sequence analysis.

[2] Seven (7) HSV 1 ARIES® negative specimens that were positive by the reference method were negative by bi-directional sequencing analysis using analytically validated primers that targeted genomic regions distinct from the ARIES® HSV 1&2 Assay. One of these specimens was positive for HSV 2 by both ARIES® and sequencing. One (1) false negative specimen was confirmed as positive for HSV-1 by bi-directional sequencing.

Summary of HSV 2 Results for Cutaneous Lesions (N=448)

ARIES® HSV 1&2 Assay	Reference Method		
	Positive	**Negative**	**Total**
Positive	96	39[1]	135
Negative	5[2]	308	313
TOTAL	101	347	448
		95% CI	
Sensitivity	95.0% (96/101)	88.8% - 98.4%	
Specificity	88.8% (308/347)	85.0% - 91.9%	

[1] Thirty five (35) HSV 2 ARIES® positive specimens that were negative by the reference method were positive by bi-directional sequencing analysis using analytically validated primers that targeted genomic regions distinct from the ARIES® HSV 1&2 Assay. The remaining four (4) false positive specimens were negative for both HSV-1 and HSV-2 by bi-directional sequencing.

[2] All five (5) HSV 2 ARIES® negative specimens that were positive by the reference method were negative by bi-directional sequencing analysis using analytically validated primers that targeted genomic regions distinct from the ARIES® HSV 1&2 Assay. Two of these specimens were positive for HSV 1 by both ARIES® and sequencing.

Summary of HSV 2 Results for Mucocutaneous Lesions (N=1453)

ARIES® HSV 1&2 Assay	Reference Method		
	Positive	**Negative**	**Total**
Positive	259	81[1]	340
Negative	4[2]	1109	1113
TOTAL	263	1190	1453
		95% CI	
Sensitivity	98.5% (250/263)	96.2% - 99.6%	
Specificity	93.2% (1109/1190)	91.6% - 94.6%	

[1] Fifty eight (58) HSV 2 ARIES® positive specimens that were negative by the reference method were positive by bi-directional sequencing analysis using analytically validated primers that targeted genomic regions distinct from the ARIES® HSV 1&2 Assay.Twenty-one (21) false positive specimens were negative for both HSV-1 and HSV-2 by bi-direc- tional sequencing. The remaining two (2) specimens were unavailable (QNS) for sequence analysis.

[2] All four (4) HSV 2 ARIES® negative specimens that were positive by the reference method were negative by bi-directional sequencing analysis using analytically validated primers that targeted genomic regions distinct from the ARIES® HSV 1&2 Assay. Three (3) of these specimens were positive for HSV 1 by both ARIES® and sequencing.

Expected Values / Reference Range:

The prevalence of HSV 1 and HSV 2 with the ARIES® HSV 1&2 Assay is calculated for cutaneous and mucocutaneous specimens and is summarized for the combined sample set per age groups and by specimen source in the tables below.

Cutaneous Prevalence by Age

Age (years)	HSV-1			HSV-2		
	Total #	**Total Positive**	**Expected Value**	**Total #**	**Total Positive**	**Expected Value**
0 - 10	10	4	40.0%	10	0	0.0%
11 - 20	53	16	30.2%	53	9	17.0%
21 - 30	125	19	15.2%	125	39	31.2%
31 - 40	85	17	20.0%	85	26	30.6%
41 - 50	63	5	7.9%	63	18	28.6%
51 - 60	50	4	8.0%	50	16	32.0%
>60	62	3	4.8%	62	27	43.5%
Not Determined	0	0	0.0%	0	0	0.0%
Overall	448	68	15.2%	448	135	30.1%

Cutaneous Prevalence by Lesion Source

Source	HSV-1			HSV-2		
	Total #	Total Positive	Expected Value	Total #	Total Positive	Expected Value
Genital - Penis	228	24	10.5%	228	74	32.5%
Skin Lesion	220	44	20.0%	220	61	27.7%
Overall	448	68	15.2%	448	135	30.1%

Mucocutaneous Prevalence by Age

Age (years)	HSV-1			HSV-2		
	Total #	Total Positive	Expected Value	Total #	Total Positive	Expected Value
0 - 10	103	14	13.6%	103	3	2.9%
11 - 20	233	78	33.5%	233	47	20.2%
21 - 30	463	114	24.6%	463	127	27.4%
31 - 40	262	54	20.6%	262	62	23.7%
41 - 50	177	23	13.0%	177	48	27.1%
51 - 60	112	12	10.7%	112	26	23.2%
>60	95	8	8.4%	95	27	28.4%
Not Determined	8	1	0.0%	8	0	0.0%
Overall	1453	304	20.9%	1453	340	23.4%

Mucocutaneous Prevalence by Lesion Source

Source	HSV-1			HSV-2		
	Total #	Total Positive	Expected Value	Total #	Total Positive	Expected Value
Anorectal / Perianal	37	3	8.1%	37	14	37.8%
Genital – Vaginal / Cervical	688	142	20.6%	688	187	27.2%
Genital – Labia / Vulva	377	71	18.8%	377	121	32.1%
Urethral	25	4	16.0%	25	4	16.0%
Nasal	45	5	11.1%	45	5	11.1%
Ocular	43	5	11.6%	43	3	7.0%
Oral	238	74	31.1%	238	6	2.5%
Overall	1453	304	20.9%	1453	340	23.4%

Conclusion:
The information submitted in this premarket notification supports the intended use of the device and demonstrates that the device is substantially equivalent to the predicate device.