# 510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
# DECISION SUMMARY

## A. 510(k) Number:

K162673

## B. Purpose for Submission:

Clearance of New Device

## C. Measurand:

Target messenger RNA (mRNA) sequences from Herpes Simplex Virus-1 (HSV-1) and Herpes Simplex Virus-2 (HSV-2)

## D. Type of Test:

An *in vitro* molecular diagnostic test for the direct, qualitative detection and differentiation of HSV-1 and HSV-2 mRNA from anogenital skin lesions

## E. Applicant:

Hologic, Inc

## F. Proprietary and Established Names:

Aptima Herpes Simplex Viruses 1 & 2 Assay

## G. Regulatory Information:

1. Regulation section: 21 CFR 866.3305
2. Classification: Class II
3. Product code: OQO
4. Panel: Microbiology (83)

## H. Intended Use:

1. Intended use(s):

   The Aptima Herpes Simplex Viruses 1 & 2 assay (Aptima HSV 1 & 2 assay) is an *in vitro* diagnostic nucleic acid amplification test (NAAT), using real time transcription-mediated amplification (TMA), for the qualitative detection and differentiation of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) messenger RNA (mRNA) in clinician-

collected swab specimens from anogenital skin lesions. The assay is intended for use with swab specimens placed in Aptima specimen transport medium (STM) or in viral transport media (VTM) that is immediately diluted into STM.

The Aptima HSV 1 & 2 assay is intended for use as an aid in the diagnosis of HSV-1 and/or HSV-2 infections in symptomatic male and female patients. The Aptima HSV 1 & 2 assay is indicated for use on the Panther® system.

**Warning**

***The Aptima HSV 1 & 2 assay is not FDA-cleared for use with cerebrospinal fluid (CSF) or for prenatal screening.***

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Panther system

## I. Device Description:

The Aptima Herpes Simplex Viruses 1 & 2 assay (Aptima HSV 1 & 2 assay) is an *in vitro* real-time nucleic acid amplification test (NAAT) for the qualitative detection and differentiation of messenger RNA (mRNA) from herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) developed for use on the fully automated Panther system. The Aptima HSV 1 & 2 assay is provided as a 100 test kit. There are 3 kits (1 assay kit, 1 controls kit, and 1 ancillary kit) that are required to perform the Aptima HSV 1 & 2 assay on the Panther system. The 3 kits and their contents are described below.

Reagents Contained in the Aptima HSV Assay Kit, Aptima HSV Controls Kit, and the Aptima Assay Fluids Kit:

| Kit | Boxes | Reagent |
|---|---|---|
| **1) Assay kit** | **Aptima HSV 1 & 2 Assay Box 1** (Refrigerated) | Amplification Reagent |
| | | Enzyme Reagent |
| | | Promoter Reagent |
| | | Internal Control Reagent |
| | **Aptima HSV 1 & 2 Assay Box 2** (Room Temperature) | Amplification Reconstitution Solution |
| | | Enzyme Reconstitution Solution |
| | | Promoter Reconstitution Solution |
| | | Target Capture Reagent |

| Kit | Boxes | Reagent |
|---|---|---|
| **2) Control kit** | **Aptima HSV 1 & 2 Controls Kit** | Negative Control |
| | | Positive Control |
| **3) Ancillary kit** | **Aptima Assay Fluids Kit** | Buffer for Deactivation Fluid |
| | | Wash |
| | | Oil |

The Aptima HSV 1 & 2 assay utilizes two collection and handling kits, which are sold independently of the assay. The collection kits described below have previously received market clearance for use in other commercialized Aptima assays:

- Aptima Multitest Swab Specimen Collection Kit (Ref: K032554), for specimens collected in VTM.
- Aptima Specimen Transfer Kit (Ref: K063664, K063451, K043224), for specimens collected in STM.

**J. Substantial Equivalence Information:**

1. Predicate device name(s): BD ProbeTec Herpes Simplex Viruses (HSV 1 & 2) Qx Amplified DNA Assays

2. Predicate 510(k) number(s): K103798

3. Comparison with predicate:

| **Similarities** | | |
|---|---|---|
| **Item** | **Aptima HSV 1 & 2 Assay (Subject Device) K162673** | **BD ProbeTec Assay (Predicate Device) K103798** |
| Intended Use | The Aptima Herpes Simplex Viruses 1 & 2 assay (Aptima HSV 1 & 2 assay) is an *in vitro* diagnostic nucleic acid amplification test (NAAT), using real time transcription-mediated amplification (TMA), for the qualitative detection and differentiation of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) messenger RNA (mRNA) in clinician-collected swab specimens from anogenital skin lesions. The assay is intended for use with swab specimens | The BD ProbeTec Herpes Simplex Viruses (HSV 1 & 2) QX Amplified DNA Assays, when tested with the BD Viper System in Extracted Mode, use Strand Displacement Amplification technology for the direct, qualitative detection and differentiation of Herpes Simplex virus type 1 (HSV1) and Herpes Simplex virus type 2 (HSV2) DNA in clinician-collected external anogenital lesion specimens. The assays are indicated for use with |

| Similarities | | |
|---|---|---|
| **Item** | **Aptima HSV 1 & 2 Assay (Subject Device) K162673** | **BD ProbeTec Assay (Predicate Device) K103798** |
| | placed in Aptima specimen transport medium (STM) or in viral transport media (VTM) that is immediately diluted into STM. The Aptima HSV 1 & 2 assay is intended for use as an aid in the diagnosis of HSV-1 and/or HSV-2 infections in symptomatic male and female patients. The Aptima HSV 1 & 2 assay is indicated for use on the Panther® system.<br><br>***Warning***: ***The Aptima HSV 1 & 2 assay is not FDA-cleared for use with cerebrospinal fluid (CSF) or for prenatal screening.*** | symptomatic individuals to aid in the diagnosis of anogenital HSV1 and HSV2 infections.<br><br>***Warning****:* The BD ProbeTec Herpes Simplex Viruses (HSV 1 & 2) QX Amplified DNA Assays (HSV QX Assays) are not FDA cleared for use with cerebrospinal fluid (CSF). The assays are not intended to be used for prenatal screening or for individuals under the age of 17 years. |
| Qualitative/ Quantitative Assay | Qualitative | Qualitative |
| Controls | Positive and negative controls. Provided as part of the Master Kit. | Positive and negative controls. Provided as part of a Master Kit. |
| Patient Population | Symptomatic male and female patients. | Symptomatic male and female patients. |
| Specimen Types | Clinician-collected swab specimens from skin lesions in the anogenital region. | Clinician-collected external anogenital lesion specimens. |

| Differences | | |
|---|---|---|
| **Item** | **Aptima HSV 1 & 2 Assay (Subject Device) K162673** | **BD ProbeTec Assay (Predicate Device) K103798** |
| Target | mRNA | DNA |
| Function | Qualitative detection and differentiation of mRNA from herpes simplex viruses 1 & 2 | Qualitative detection and differentiation of DNA from herpes simplex viruses 1 & 2 |
| Technology | The subject assay is comprised of a nucleic acid amplification | The predicate assay is comprised of an amplification test for use |

| Differences | | |
|---|---|---|
| **Item** | **Aptima HSV 1 & 2 Assay (Subject Device) K162673** | **BD ProbeTec Assay (Predicate Device) K103798** |
| | test (NAAT) for use on the automated Panther system, that utilizes target capture to extract viral mRNA from patient samples, and real-time transcription mediated amplification (TMA) and detection of HSV-1, and HSV-2 mRNAs and an internal control RNA. | on the automated BD Viper System that utilizes non-specific extraction of DNA from clinical specimens, followed by binding of DNA to magnetic particles, washing of the bound nucleic acid and elution in an amplification-compatible buffer. When present, HSV1 and/or 2 DNA is detected by Strand Displacement Amplification (SDA) of type-specific target sequences in the presence of a fluorescently labeled detector probe. |
| Platform | The Panther system is an *in vitro* diagnostic device intended for use in clinical laboratories by trained laboratory professionals for the automation of NAATs. The Panther system provides automation of all assay steps, including sample processing, amplification of target nucleic acid, amplicon detection, data reduction, and amplicon inactivation. | BD Viper System is an in vitro diagnostic device intended for use in clinical laboratories by trained laboratory professionals for the automation of NAATs. The BD Viper System provides automated non-specific extraction and amplification of DNA from clinical specimens. In Extracted Mode, it uses Strand Displacement Amplification technology. When present, HSV 1 and/or 2 amplicon is detected by Strand Displacement Amplification. |
| Specimen Collection | • Aptima Multitest Swab Specimen Collection Kit (STM).<br>• Aptima Specimen Transfer Kit (for use with specimens collected in VTM) | • BD ProbeTec$Q^x$ Collection Kit for Endocervical or Lesion Specimens<br>• BD Universal Viral Transport Medium (VTM) w/Swab Collection Kit<br>• Copan Universal Transport Medium w/Swab Collection Kit (same as BD VTM Kit) |

**K. Standard/Guidance Document Referenced (if applicable):** Not Applicable

**L. Test Principle:**

The Aptima HSV 1 & 2 assay involves three main steps, which all take place in a single tube on the Panther system: target capture, target amplification by real time transcription-mediated amplification (TMA), and detection of the amplification products (amplicons) by the fluorescent labeled probes (torches). The assay incorporates an Internal Control (IC) in every test to monitor targeted nucleic acid capture, amplification and detection.

Target capture:
When the Aptima HSV 1 & 2 assay is performed, the targeted viral mRNA and IC are isolated using magnetic microparticles and target-specific capture oligomers, in a process called target capture. The capture oligomers contain sequences complementary to specific regions of the targeted RNA (HSV mRNA or IC) as well as a string of deoxyadenosine residues. During the hybridization step, the sequence-specific regions of the capture oligomers bind to specific regions of the RNA target molecules. The microparticles, including the captured RNA target molecules bound to them, are pulled to the side of the reaction tube using magnets and the supernatant is aspirated. The particles are washed to remove residual specimen matrix that may contain amplification inhibitors. After target capture steps are completed, the specimens are ready for amplification.

Target Amplification by TMA:
Target amplification occurs via TMA, which is a transcription-based nucleic acid amplification method that utilizes two enzymes, MMLV (Moloney murine leukemia virus) reverse transcriptase and T7 RNA polymerase. The reverse transcriptase is used to generate a DNA copy (containing a promoter sequence for T7 RNA polymerase) of the target sequence. T7 RNA polymerase produces multiple copies of RNA amplicon from the DNA copy template.

Detection:
Detection is achieved using single-stranded nucleic acid torches that are present during the amplification of the target and hybridize specifically to the amplicon in real time. Each torch has a fluorophore and a quencher. The quencher suppresses the fluorescence of the fluorophore as it is designed to be in close proximity when not hybridized to the amplicon. When the torch binds to the amplicon, the quencher is moved farther away from the fluorophore and it will emit a signal at a specific wavelength when excited by a light source. More of the torches hybridize when more amplicon is present. The increase in fluorescent signal from progressive amplification is detected by fluorometers within the Panther system. The Panther system can detect and discriminate between the three fluorescent signals corresponding to HSV-1, HSV-2 and IC amplification products. The fluorescence (measured in relative fluorescence units [RFU]) is monitored over time to produce a real-time fluorescence emergence curve for each reporter dye. The Panther system software compares the fluorescence emergence curves to fixed cut off times to report results (TTime) for HSV-1, HSV-2 and IC.

Test Interpretation:
Test results are automatically determined by the assay software. Results for HSV-1 and HSV-2 detection are reported separately. Table 1 shows the possible results reported in a valid run and result interpretations. Samples with invalid test results should be retested. The first valid result should be reported.

**Table 1: Test Results and Interpretation:**

| HSV-1 Result | HSV-2 Result | Interpretation |
|---|---|---|
| HSV1 neg | HSV2 neg | Negative: No HSV-1 or HSV-2 mRNA detected |
| HSV1 neg | HSV2 POS | HSV-2 positive: HSV-2 mRNA detected |
| HSV1 POS | HSV2 neg | HSV-1 positive: HSV-1 mRNA detected |
| HSV1 POS | HSV2 POS | HSV-1 and HSV-2 positive: HSV-1 and HSV-2 mRNA detected |
| Invalid | Invalid | Invalid: There was an error in the generation of the result. Specimen should be retested. |

## M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Reproducibility:*

   Aptima HSV 1 & 2 assay reproducibility was evaluated at three external US sites. Testing was performed using three lots of assay reagents and six operators (two at each site). At each site, testing was performed for at least six days where two operators each performed two runs per day over at least three days with one operator performing testing each day. Panel members were created by spiking HSV-1 and/or HSV-2 viral particles into neat STM and three replicates of each panel member were tested in each run. Final HSV-1 concentrations ranged from 0 TCID50/mL to 86.96 TCID50/mL and final HSV-2 concentrations ranged from 0 TCID50/mL to 1.63 TCID50/mL; agreement with expected results is presented in Table 2. Table 3 summarizes the TTime results for panel members containing low and moderate levels of HSV-1 and HSV-2 and Table 4 summarizes the TTime results for the Positive Control.

**Table 2: Reproducibility - Agreement of Aptima HSV 1 & 2 Assay with Expected Results**

| Level | | Target Conc ($TCID_{50}$/mL) | | Expected Result | | N | Agreed (N) | | Agreement (%) (95% CI) | |
|---|---|---|---|---|---|---|---|---|---|---|
| HSV-1 | HSV-2 | HSV-1 | HSV-2 | HSV-1 | HSV-2 | | HSV-1 | HSV-2 | HSV-1 | HSV-2 |
| Neg | Neg | 0 | 0 | Neg | Neg | 108 | 108 | 108 | 100 (96.6-100) | 100 (96.6-100) |
| LPos | Neg | 28.90* | 0 | Pos | Neg | 108 | 103 | 108 | 95.4 (89.6-98.0) | 100 (96.6-100) |
| Neg | LPos | 0 | 0.54* | Neg | Pos | 108 | 108 | 105 | 100 (96.6-100) | 97.2 (92.1-99.1) |
| LPos | MPos | 28.90* | 1.63 | Pos | Pos | 108 | 97 | 108 | 89.8 (82.7-94.2) | 100 (96.6-100) |
| MPos | LPos | 86.96 | 0.54* | Pos | Pos | 108 | 108 | 108 | 100 (96.6-100) | 100 (96.6-100) |
| HNeg | Neg | 3.00 | 0 | Pos | Neg | 108 | 50 | 108 | 46.3 (37.2-55.7) | 100 (96.6-100) |
| Neg | HNeg | 0 | 0.20 | Neg | Pos | 108 | 108 | 86 | 100 (96.6-100) | 79.6 (71.1-86.1) |

CI = confidence interval, Conc = concentration, HNeg = high negative (<1 X LoD), LPos = low positive (1-2 X LoD), MPos = moderate positive (2-3 X LoD), Neg = negative, Pos = positive,
*LoD values for HSV-1 and HSV-2 in neat STM were 28.90 and 0.54 $TCID_{50}$/mL, respectively.

**Table 3: Reproducibility - Signal Variability of the Aptima HSV 1 & 2 Assay in Low and Moderate Panel Members**

| | Virus Level | N | Mean TTime | Between Sites | Between Lots | Between Operators/ Days[1] | Between Runs | Within Runs | Total |
|---|---|---|---|---|---|---|---|---|---|
| | | | | SD (%CV) | SD (%CV) | SD (%CV) | SD (%CV) | SD (%CV) | SD (%CV) |
| HSV-1 | LPos | 103 | 24.68 | 0 (0) | 1.63 (6.62) | 0.75 (3.04) | 0.54 (2.18) | 0.88 (3.55) | 2.07 (8.40) |
| | LPos | 97 | 23.91 | 0 (0) | 2.18 (9.11) | 0.86 (3.58) | 0 (0) | 1.60 (6.71) | 2.84 (11.87) |
| | MPos | 108 | 22.96 | 0 (0) | 1.54 (6.69) | 0.38 (1.65) | 0.68 (2.96) | 0.94 (4.11) | 1.96 (8.55) |
| HSV-2 | LPos | 105 | 25.49 | 0 (0) | 0.84 (3.30) | 0.70 (2.74) | 0 (0) | 2.52 (9.87) | 2.74 (10.76) |
| | LPos | 108 | 25.34 | 0 (0) | 1.54 (6.08) | 0.86 (3.41) | 0.59 (2.34) | 2.67 (10.53) | 3.26 (12.85) |
| | MPos | 108 | 22.91 | 0 (0) | 1.09 (4.76) | 0.35 (1.53) | 0.42 (1.83) | 1.06 (4.64) | 1.62 (7.07) |

Conc = concentration, CV = coefficient of variation, LPos = low positive (1-2 X LoD), MPos = moderate positive (2-3 X LoD), SD = standard deviation

Note: Variability from some factors may be numerically negative. This can occur if the variability due to those factors is very small. In these cases, SD and CV are shown as 0.

[1]Between Operators may be confounded with Between Days; therefore, Between Operators and Between Days estimates are combined in Between Operators/Days.

**Table 4: Reproducibility - Signal Variability of the Aptima HSV 1 & 2 Assay in the Positive Control**

| Virus | N | Mean TTime | Between Sites | Between Lots | Between Operators/ Days[1] | Within Days | Total |
|---|---|---|---|---|---|---|---|
| | | | SD (%CV) | SD (%CV) | SD (%CV) | SD (%CV) | SD (%CV) |
| HSV-1 | 36 | 20.11 | 0 (0) | 1.30 (6.48) | 0.40 (1.99) | 1.09 (5.42) | 1.75 (8.68) |
| HSV-2 | 36 | 22.16 | 0 (0) | 1.61 (7.27) | 0.71 (3.21) | 1.38 (6.22) | 2.24 (10.09) |

CV = coefficient of variation, SD = standard deviation

Note: Variability from some factors may be numerically negative. This can occur if the variability due to those factors is very small. In these cases, SD and CV are shown as 0.

[1]Between Operators may be confounded with Between Days; therefore, Between Operators and Between Days estimates are combined in Between Operators/Days.

*b. Linearity/assay reportable range:*

Not Applicable.

*c. Traceability, Stability, Expected values (controls, calibrators, or methods):*

Internal Control

The IC consists of a random sequence of RNA unrelated to HSV 1 or HSV 2 . The IC is added to each specimen aliquot during sample preparation and is amplified in the same reaction as the HSV-1 and HSV-2 mRNA targets. It is used to determine the validity of each individual reaction and as an indicator of analyte capture, amplification and/or detection errors, as well as to control for operator and instrument errors.

External Assay Controls

Two controls are provided separately by Hologic to the user in the Aptima HSV Controls Kit: one HSV1/HSV2 dual positive control and one negative control. The positive control is composed of known concentrations of in vitro transcripts (IVT) corresponding to HSV-1 and HSV-2 UL42 mRNAs. These controls must generate results within predefined specifications to be valid. The negative control must also provide a valid negative result for the run to be valid. Additionally, both controls must generate IC results within predefined specifications.

*d. Detection limit:*

(i) Analytical Sensitivity (Limit of Detection) in Clinical Specimen Matrix:

The Limit of Detection (LoD) of the Aptima HSV 1 & 2 assay was determined by testing a series of panels consisting of HSV-1 or HSV-2 diluted in pooled negative clinical specimens collected in one of two transport media: 1) STM and 2) VTM. For HSV-1, MacIntyre and HF viral strains were tested. For HSV-2, MS and G strains were tested. At least 60 replicates were tested at each concentration for each panel member for each matrix and virus strain across 3 reagents lots. The LoD for each strain and specimen type was calculated using Probit analysis and summarized in Table 5.

**Table 5: LoD of the Aptima HSV 1 & 2 Assay in VTM and STM**

| HSV Type/Strain | Media Type | LoD TCID50/mL |
|---|---|---|
| HSV-1 MacIntyre | STM | 60.6 |
| | VTM | 186.9 |
| HSV-1 HF | STM | 78.9 |
| | VTM | 159.3 |
| HSV-2 MS | STM | 18.2 |
| | VTM | 28.7 |
| HSV-2 G | STM | 18.8 |
| | VTM | 128.8 |

(ii) LoD Verification:

The LoD was verified using two clinical isolates of HSV-1 and two clinical isolates of HSV-2 in both VTM and STM. Each HSV clinical isolate was tested with the Aptima HSV 1 & 2 assay using 60 replicates each at 3 concentrations (1X LoD, 3X LoD, and 10X LoD, see Table 6 for LoD values). Testing was completed in both STM and VTM matrix for all four clinical isolates and was conducted using 3 lots of reagents. All replicates for all clinical isolates at all three concentrations tested were detected by the Aptima HSV 1 & 2 assay, demonstrating that the assay can detect a range of both HSV-1 and HSV-2 clinical isolates at the determined LoD.

**Table 6: HSV 1 and HSV 2 LoD**

| HSV Type | Media Type | LoD (TCID50/mL) |
|---|---|---|
| HSV-1 | STM | 78.9 |
| | VTM | 186.9 |
| HSV-2 | STM | 18.8 |
| | VTM | 128.8 |

e. *Analytical specificity:*

Potential cross-reactivity to the non-targeted micro-organisms listed in Table 7 was

evaluated in the Aptima HSV 1 & 2 assays. Panel members were prepared by spiking the potentially cross-reacting microorganisms into STM and then these panels were divided into 3 groups: 1) unspiked, 2) HSV-1 spiked to a concentration of 3X LoD, and 3) HSV-2 spiked to a concentration of 3X LoD. Group 1 was used to test for cross-reactivity while Groups 2 and 3 were used to test for microbial interference. No cross-reactivity or interference in the performance of the assay was observed in the presence of the microorganisms tested.

**Table 7: Cross-Reactivity and Microbial Interference Panel**

| Microorganism | Concentration |
|---|---|
| *Acinetobacter calcoaceticus* | $1x10^6$ CFU/mL[1,2] |
| *Acinetobacter lwoffii* | $1x10^6$ CFU/mL[1,2] |
| *Actinomyces israelii* | $1x10^6$ RNA copies /mL[2] |
| Adenovirus type 1 | $1x10^5$ TCID50/mL[3] |
| *Alcaligenes faecalis* | $1x10^6$ CFU/mL[1] |
| *Atopobium vaginae* | $1x10^6$ RNA copies /mL[2] |
| *Bacteroides fragilis* | $1x10^6$ CFU/mL[1,2] |
| *Bifidobacterium adolescentis* | $1x10^6$ CFU/mL[1,2] |
| BK virus | $1x10^5$ DNA copies/mL[3] |
| *Bordetella bronchiseptica* | $1x10^6$ CFU/mL[1,2] |
| *Bordetella pertussis* | $1x10^6$ CFU/mL[1,2] |
| *Campylobacter jejuni* | $1x10^6$ CFU/mL[1,2] |
| *Candida glabrata* | $1x10^6$ CFU/mL[1,2] |
| *Clostridium difficile* | $1x10^6$ CFU/mL[1,2] |
| *Clostridium perfringens* | $1x10^6$ CFU/mL[1,2] |
| *Corynebacterium genitalium* | $1x10^6$ CFU/mL[1,2] |
| *Cryptococcus neoformans* | $1x10^6$ CFU/mL[1,2] |
| *Enterobacter aerogenes* | $1x10^6$ CFU/mL[1,2] |
| *Enterobacter cloacae* | $1x10^6$ CFU/mL[1,2] |
| *Enterococcus faecium* | $1x10^6$ CFU/mL[1,2] |
| *Enterococcus faecalis* | $1x10^6$ CFU/mL[1,2] |
| Epstein-Barr virus | $1x10^5$ DNA copies/mL[3] |
| *Escherichia coli* | $1x10^6$ CFU/mL[1,2] |
| *Fusobacterium nucleatum* | $1x10^6$ CFU/mL[1,2] |
| *Gardnerella vaginalis* | $1x10^6$ CFU/mL[1,2] |
| *Haemophilus ducreyi* | $1x10^6$ CFU/mL[1,2] |
| Hepatitis B virus | $1x10^5$ IU/mL[4,3] |
| *Klebsiella pneumoniae* | $1x10^6$ CFU/mL[1,2] |
| *Lactobacillus crispatus* | $1x10^6$ CFU/mL[1,2] |

| Microorganism | Concentration |
|---|---|
| *Moraxella catarrhalis* | $1x10^6$ CFU/mL[1,2] |
| *Mycoplasma hominis* | $1x10^6$ RNA copies /mL[2] |
| *Mycoplasma orale* | $1x10^6$ RNA copies /mL[2] |
| *Neisseria gonorrhoeae* | $1x10^6$ CFU/mL[1,2] |
| *Neisseria meningitidis* | $1x10^6$ CFU/mL[1,2] |
| Parvovirus B19 | $1x10^5$ TCID50/mL[3] |
| *Prevotella bivia* | $1x10^6$ CFU/mL[1,2] |
| *Propionibacterium acnes* | $1x10^6$ CFU/mL[1,2] |
| *Proteus mirabilis* | $1x10^6$ CFU/mL[1,2] |
| *Proteus vulgaris* | $1x10^6$ CFU/mL[1,2] |
| *Pseudomonas aeruginosa* | $1x10^6$ CFU/mL[1,2] |
| *Staphylococcus aureus* | $1x10^6$ CFU/mL[1,2] |
| *Staphylococcus epidermidis* | $1x10^6$ CFU/mL[1,2] |
| *Staphylococcus saprophyticus* | $1x10^6$ CFU/mL[1,2] |
| *Streptococcus mitis* | $1x10^6$ CFU/mL[1,2] |
| *Streptococcus pneumonia** | $1x10^5$ CFU/mL[1,2] |
| *Streptococcus pyogenes* | $1x10^6$ CFU/mL[1,2] |
| Varicella-zoster virus | $1x10^5$ DNA copies/mL[3] |
| West Nile virus | $1x10^5$ TCID50/mL[3] |

[1]CFU = Colony Forming Units, [2]Procured internally from Hologic, Inc.,[3]Obtained from ZeptoMetrix Corporation (Buffalo NY), [4]IU=International Units
*Cross reactivity was observed in Streptococcus pneumoniae at $1x10^6$ CFU/mL

*f. Interfering Studies*

The susceptibility of the Aptima HSV 1 & 2 assay to interference by elevated levels of potentially interfering substances that may be present in clinical specimens was evaluated. HSV negative samples and samples spiked to a test concentration of ~3X LoD of HSV-1 Macintyre virus or HSV-2 MS virus were tested. No interference in performance of the Aptima HSV 1 & 2 assay was observed in the presence of a representative brand of the following exogenous and endogenous substances at the concentrations stated in Table 8.

**Table 8: Interfering Substances**

| Substance | Brand/Source | Final Concentration |
|---|---|---|
| Vaginal lubricant | KY Jelly | 5% V/V |
| Spermicide/contraceptive jelly | Options Gynol II | 4% W/V |
| Anti-fungal cream | Monistat 3 | 5% W/V |
| Douche | Up & Up Feminine Wash | 5% V/V |
| Feminine spray | FDS Feminine Deodorant Spray | 5% W/V |
| Body lotion | Vaseline Aloe Fresh | 5% W/V |
| Powder | Summer's Eve Powder | 5% W/V |
| Glacial acetic acid wash solution | Glacial acetic acid wash solution | 5% V/V |
| Hemorrhoid cream | Preparation H | 5% W/V |
| Urine | In-house urine collection | 5% V/V |
| Whole blood | In-house whole blood collection | 0.5% V/V |
| Leukocytes | Biological Specialty Corporation Leukocytes | $4x10^5$ cells/mL |
| Mucus | Sigma Aldrich Mucine | 0.3% W/V |
| Seminal fluid | Seminal fluid | 5% V/V |
| Feces | Feces | 0.03% W/V |
| Protein | Casein | 4% W/V |
| Antiviral drug | Acyclovir | 5% W/V |

g. *Specimen Stability in Viral Transport Medium (VTM) and Aptima Specimen Transport Medium (STM)*

The specimen stability was assessed with naturally occurring positive clinical specimens in both VTM (diluted in STM ) and neat STM that were placed at various temperatures over a period of time (30°C for 30 days, 2-8°C for 30 days, -20°C for 60 days, and -70°C for 60 days) and subsequently tested with the Aptima HSV 1 & 2 assay.

In addition, each transport medium was spiked with HSV-1 MacIntyre strain and HSV-2 MS strain at 3X and 10X LoD and tested, in duplicate, at the following temperatures and intervals: 30°C for ≥ 30 days, 2-8°C for ≥ 30 days, -20°C for ≥ 30 days and -70°C for ≥ 30 days.

For the specimen freeze and thaw study, stability was assessed by alternately freezing specimens at -20°C or -70°C and then thawing at room temperature for a total of 3 additional freeze-thaw cycles before being tested again in the Aptima HSV 1 & 2 assay in duplicate.

The study data support the stability claims for HSV-1 and HSV-2 specimens collected in STM and stored at 2°C to 30°C for up to 36 days and at -20°C to -70°C for up to 36 days. The study data also support the stability claims for HSV-1 and HSV-2

specimens collected in VTM, immediately transferred to STM, and then stored at 2°C to 30°C for up to 30 days and at -20°C to -70°C for up to 36 days. Specimens collected directly in STM or collected in VTM and then immediately transferred to STM may be frozen and thawed up to 3 times prior to testing.

*h. Competitive Inhibition*

Competitive inhibition was evaluated to assess the ability of the Aptima HSV 1 & 2 assay to detect HSV 1 and HSV 2 analytes when both are present in the same specimen. Low and high titer concentrations of HSV-1 viral particles were tested in combination with low, moderate, and high concentrations of HSV-2 virus. Panel composition and concentrations are listed in Table 9. All testing resulted in 100% detection for both HSV-1 and HSV-2.

**Table 9: Panels Co-infected with Varying Titers of HSV-1 and HSV-2**

| Panel Member | HSV-1 Concentration | HSV-2 Concentration |
|---|---|---|
| HSV-1 Low; HSV-2 Low | 86.7 $TCID_{50}/mL$[1] | 1.62 $TCID_{50}/mL$[2] |
| HSV-1 Low; HSV-2 Moderate | 86.7 $TCID_{50}/mL$[1] | 540 $TCID_{50}/mL$[3] |
| HSV-1 High; HSV-2 Low | 28,900 $TCID_{50}/mL$[4] | 1.62 $TCID_{50}/mL$[2] |
| HSV-1 High; HSV-2 Moderate | 28,900 $TCID_{50}/mL$[4] | 540 $TCID_{50}/mL$[3] |
| HSV-1 Low; HSV-2 High | 86.7 $TCID_{50}/mL$[1] | 9,000 $TCID_{50}/mL$[5] |

[1]3X LoD HSV-1; [2]3X LoD HSV-2; [3]1000X LoD HSV-2; [4]1000X LoD HSV-1; [5]16667X LoD HSV-2.

*i. Assay cut-off:* Not Applicable

2. Comparison studies:

*a. Method comparison with predicate device:*

The clinical performance evaluation was performed against a composite reference method comprised of the ELVIS HSV ID and D3 Typing Test system viral culture and a validated PCR/ bidirectional sequencing procedure. A third FDA cleared assay was used when the ELVIS D3 culture and PCR/sequencing results did not agree on the type of HSV detected or when PCR/sequencing detected both HSV-1 and HSV-2. See Clinical Study Section below (Section 3).

*b. Matrix comparison:* Not applicable

3. Clinical studies:

*a. Clinical Sensitivity:* Not applicable

*b. Clinical specificity:* Not applicable

*c. Other clinical supportive data (when a. and b. are not applicable):*

The performance of the Aptima HSV 1 & 2 assay was compared with a composite reference method: the ELVIS HSV ID and D3 Typing Test System (Diagnostic Hybrids, Inc.; K091753), and a validated PCR/ bidirectional sequencing procedure. A third FDA cleared assay was used when the ELVIS D3 culture and PCR/sequencing results did not agree on the type of HSV detected or when PCR/sequencing detected both HSV-1 and HSV-2.

Note: The ELVIS D3 culture method cannot detect type HSV-1 if the sample is positive for HSV-2, thus, the method cannot detect HSV-1 and HSV-2 co-infected samples.

**Clinical Performance:**

A prospective, multicenter clinical study was conducted to establish the performance characteristics of the Aptima HSV 1 & 2 assay. A total of 544 evaluable subjects (195 males and 349 females) with active anogenital lesions were enrolled from 17 US clinical sites, including family planning, dermatology, pediatrics/adolescent, sexually transmitted infection, private practice, public health clinics, hospitals, universities, and clinical research sites.

Two (2) swab specimens were collected from a single lesion from each subject: one was collected with a swab from a commercially available VTM collection kit and one was collected with a swab from the Aptima Multitest Swab Specimen Collection Kit (STM). Specimens were processed in accordance with the appropriate package insert instructions. Aptima HSV 1 & 2 assay testing was performed at 3 external sites. The performance of the Aptima HSV-1 & 2 assay was evaluated relative to the composite reference method specified above. The performance of the Aptima HSV 1 & 2 assay was estimated for detection of HSV-1 and HSV-2 separately using each specimen type.

For HSV-1, of the 544 evaluable subjects, 528 VTM and 531 STM specimen types resulted in evaluable results for HSV-1 analysis (16 VTM and 13 STM were reported as unknown composite reference interpretation).For HSV-2, of the 544 evaluable subjects, 533 VTM and 535 STM specimen types produced evaluable results for HSV-2 analysis (11 VTM and 9 STM were reported as unknown composite reference interpretation).

The performance of the Aptima HSV 1 & 2 assay compared to the composite reference method for anogenital skin lesion specimens collected in STM and VTM is summarized in Tables 10 and 11. The overall sensitivity for HSV-1 was 93.4% for VTM and 94.7% for STM specimen types and the specificity was 99.8% for VTM and 99.6% for STM specimen types (Table 10). For HSV-2, the sensitivity was 96.9% for VTM and 98.4% for STM specimen types and the specificity was 97.5% for VTM and 92.8% for STM specimen types (Table 11).

## Table 10: Summary of HSV-1 Results by VTM and STM Specimen Type

| Specimen Type | Gender | N | TP | FP | TN | FN | Prev (%) | Sensitivity % (95% CI)[1] | Specificity % (95% CI)[1] | PPV % (95% CI)[2] | NPV % (95% CI)[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| VTM | Combined | 528 | 71 | 1[3] | 451 | 5[4] | 14.4 | 93.4 (85.5-97.2) | 99.8 (98.8-99.9) | 98.6 (93.0-100) | 98.9 (97.6-99.6) |
| | Male | 192 | 19 | 1 | 170 | 2 | 10.9 | 90.5 (71.1-97.3) | 99.4 (96.8-99.9) | 95.0 (78.6-99.8) | 98.8 (96.4-99.9) |
| | Female | 336 | 52 | 0 | 281 | 3 | 16.4 | 94.5 (85.1-98.1) | 100 (98.7-100) | 100 (93.7-100) | 98.9 (97.1-99.8) |
| STM | Combined | 531 | 71 | 2[5] | 454 | 4[6] | 14.1 | 94.7 (87.1-97.9) | 99.6 (98.4-99.9) | 97.3 (91.1-99.6) | 99.1 (97.9-99.8) |
| | Male | 192 | 20 | 2 | 169 | 1 | 10.9 | 95.2 (77.3-99.2) | 98.8 (95.8-99.7) | 90.9 (74.5-98.7) | 99.4 (97.2-100) |
| | Female | 339 | 51 | 0 | 285 | 3 | 15.9 | 94.4 (84.9-98.1) | 100 (98.7-100) | 100 (93.6-100) | 99.0 (97.2-99.8) |

STM = Aptima Multitest Swab specimen, Prev = prevalence, VTM = VTM sample

[1]CI: confidence interval.

[2]PPV 95% CI computed from the exact 95% CI for the positive likelihood ratio, NPV 95% CI computed from the exact 95% CI for the negative likelihood ratio.

[3]The sample had a negative culture result.

[4]Two samples had negative culture results, one had a non-typable HSV positive culture result, and two were HSV-1 positive by culture.

[5]Both specimens had negative culture results.

[6]One specimen had a negative culture result, one had a non-typable HSV positive culture result, and two were HSV-1 positive by culture.

## Table 11: Summary of HSV-2 Results by VTM and STM Specimen Type

| Specimen Type | Gender | N | TP | FP | TN | FN | Prev (%) | Sensitivity % (95% CI)[1] | Specificity % (95% CI)[1] | PPV % (95% CI)[2] | NPV % (95% CI)[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| VTM | Combined | 533 | 248 | 7[3] | 270 | 8[4] | 48.0 | 96.9 (94.0-98.4) | 97.5 (94.9-98.8) | 97.3 (94.7-98.8) | 97.1 (94.6-98.7) |
| | Male | 194 | 79 | 2 | 110 | 3 | 42.3 | 96.3 (89.8-98.7) | 98.2 (93.7-99.5) | 97.5 (92.0-99.7) | 97.3 (93.0-99.4) |
| | Female | 339 | 169 | 5 | 160 | 5 | 51.3 | 97.1 (93.5-98.8) | 97.0 (93.1-98.7) | 97.1 (93.8-99.0) | 97.0 (93.4-99.0) |
| STM | Combined | 535 | 253 | 20[5] | 258 | 4[6] | 48.0 | 98.4 (96.1-99.4) | 92.8 (89.1-95.3) | 92.7 (89.4-95.3) | 98.5 (96.3-99.6) |
| | Male | 194 | 79 | 6 | 106 | 3 | 42.3 | 96.3 (89.8-98.7) | 94.6 (88.8-97.5) | 92.9 (86.5-97.1) | 97.2 (92.8-99.4) |
| | Female | 341 | 174 | 14 | 152 | 1 | 51.3 | 99.4 (96.8-99.9) | 91.6 (86.3-94.9) | 92.6 (88.5-95.7) | 99.3 (96.6-100) |

STM = Aptima Multitest Swab specimen, Prev = prevalence, VTM = VTM sample

[1] CI: confidence interval.

[2]PPV 95% CI computed from the exact 95% CI for the positive likelihood ratio, NPV 95% CI computed from the exact 95% CI for the negative likelihood ratio

[3]Six samples had negative culture results and one was HSV-1 positive by culture.

[4]All eight samples had negative culture results.

[5]Eighteen specimens had negative culture results and two were HSV-1 positive by culture.

[6]All four specimens had negative culture results

4. Clinical cut-off: N/A

5. Expected values/Reference range:
**Prevalence:** The prevalence of HSV-1 and HSV-2 observed during the multi-center clinical study was calculated for the Aptima HSV 1 & 2 assay. The prevalence of HSV-1 and HSV-2 with the Aptima HSV 1 & 2 assay is summarized by age group, gender group, and specimen type in Table 12.

**Table 12: Gender and Age Distribution by VTM and STM Specimen Type[1]**

| Gender Age Group | %Prevalence (# positive results/# tested) | | | |
|---|---|---|---|---|
| | VTM | | STM | |
| | HSV-1 | HSV-2 | HSV-1 | HSV-2 |
| **Male** | | | | |
| All ages | 10.4 (20/192) | 41.8 ( 81/194) | 11.5 (22/192) | 43.8 (85/194) |
| < 2 years | 0.0 (0/0) | 0.0 (0/0) | 0.0 (0/0) | 0.0 (0/0) |
| 2 to 11 years | 0.0 (0/1) | 0.0 (0/1) | 0.0 (0/1) | 0.0 (0/1) |
| 12 to 21 years | 11.1 (2/18) | 38.9 (7/18) | 11.1 (2/18) | 38.9 (7/18) |
| 22 to 30 years | 14.0 (13/93) | 34.0 (32/94) | 14.9 (14/94) | 35.8 (34/95) |
| 31 to 40 years | 12.5 (5/40) | 50.0 (20/40) | 12.8 (5/39) | 53.8 (21/39) |
| 41 to 50 years | 0.0 (0/20) | 52.4 (11/21) | 0.0 (0/20) | 52.4 (11/21) |
| 51 to 60 years | 0.0 (0/14) | 57.1 (8/14) | 7.1 (1/14) | 57.1 (8/14) |
| > 60 years | 0.0 (0/6) | 50.0 (3/6) | 0.0 (0/6) | 66.7 (4/6) |
| **Female** | | | | |
| All ages | 15.5 (52/336) | 51.3 (174/339) | 15.0 (51/339) | 55.1 (188/341) |
| < 2 years | 0.0 (0/1) | 0.0 (0/1) | 0.0 (0/1) | 0.0 (0/1) |
| 2 to 11 years | 0.0 (0/0) | 0.0 (0/0) | 0.0 (0/0) | 0.0 (0/0) |
| 12 to 21 years | 23.8 (15/63) | 56.3 (36/64) | 23.1 (15/65) | 59.1 (39/66) |
| 22 to 30 years | 14.6 (25/171) | 52.6 (90/171) | 14.5 (25/172) | 56.4 (97/172) |
| 31 to 40 years | 11.1 (7/63) | 46.0 (29/63) | 12.5 (8/64) | 47.6 (30/63) |
| 41 to 50 years | 18.2 (4/22) | 39.1 (9/23) | 10.0 (2/20) | 47.6 (10/21) |
| 51 to 60 years | 7.7 (1/13) | 46.2 (6/13) | 7.1 (1/14) | 57.1 (8/14) |
| > 60 years | 0.0 (0/3) | 100 (4/4) | 0.0 (0/3) | 100 (4/4) |
| **Combined** | | | | |
| All ages | 13.6 (72/528) | 47.8 (255/533) | 13.7 (73/531) | 51.0 (273/535) |
| < 2 years | 0.0 (0/1) | 0.0 (0/1) | 0.0 (0/1) | 0.0 (0/1) |
| 2 to 11 years | 0.0 (0/1) | 0.0 (0/1) | 0.0 (0/1) | 0.0 (0/1) |
| 12 to 21 years | 21.0 (17/81) | 52.4 (43/82) | 20.5 (17/83) | 54.8 (46/84) |
| 22 to 30 years | 14.4 (38/264) | 46.0 (122/265) | 14.7 (39/266) | 49.1 (131/267) |
| 31 to 40 years | 11.7 (12/103) | 47.6 (49/103) | 12.6 (13/103) | 50.0 (51/102) |
| 41 to 50 years | 9.5 (4/42) | 45.5 (20/44) | 5.0 (2/40) | 50.0 (21/42) |
| 51 to 60 years | 3.7 (1/27) | 51.9 (14/27) | 7.1 (2/28) | 57.1 (16/28) |
| > 60 years | 0.0 (0/9) | 70.0 (7/10) | 0.0 (0/9) | 80.0 (8/10) |

[1]No subjects had positive Aptima HSV 1 & 2 assay results for both HSV-1 and HSV-2.

**Positive and Negative Predicted Value**: The estimated positive and negative predictive values (PPV and NPV) of the Aptima HSV 1 & 2 assay for detection of HSV-1 and HSV-2 across different hypothetical prevalence rates are shown for each specimen type in Table 13. These calculations are based on the overall estimated sensitivity and specificity for each specimen type as determined in the clinical performance study.

**Table 13: Prevalence vs Hypothetical PPV[1] and NPV[2] for Detection of HSV-1 and HSV-2 by Specimen Type**

| Specimen Type | Prevalence (%) | HSV-1 | | HSV-2 | |
|---|---|---|---|---|---|
| | | PPV (%) | NPV (%) | PPV (%) | NPV (%) |
| VTM | 1 | 81.0 | 99.9 | 27.9 | 100 |
| | 2 | 89.6 | 99.9 | 43.9 | 99.9 |
| | 5 | 95.7 | 99.7 | 66.9 | 99.8 |
| | 10 | 97.9 | 99.3 | 81.0 | 99.6 |
| | 20 | 99.1 | 98.4 | 90.6 | 99.2 |
| | 30 | 99.5 | 97.3 | 94.3 | 98.6 |
| | 40 | 99.6 | 95.8 | 96.2 | 97.9 |
| | 50 | 99.8 | 93.8 | 97.5 | 96.9 |
| STM | 1 | 68.6 | 99.9 | 12.1 | 100 |
| | 2 | 81.5 | 99.9 | 21.8 | 100 |
| | 5 | 91.9 | 99.7 | 41.9 | 99.9 |
| | 10 | 96.0 | 99.4 | 60.3 | 99.8 |
| | 20 | 98.2 | 98.7 | 77.4 | 99.6 |
| | 30 | 98.9 | 97.8 | 85.4 | 99.3 |
| | 40 | 99.3 | 96.6 | 90.1 | 98.9 |
| | 50 | 99.5 | 94.9 | 93.2 | 98.4 |

STM = Aptima Multitest swab specimen, VTM = VTM sample

[1]PPV was calculated using:
(Sensitivity x Prevalence) / (Sensitivity x Prevalence + [1 - Specificity] x [1 - Prevalence]).

[2]NPV was calculated using:
(Specificity x [1 - Prevalence]) / ([1 - Sensitivity] x Prevalence + Specificity x [1 - Prevalence]).

**TTime Distribution for Aptima HSV 1 & 2 Assay Positive Controls**
The distribution of the TTime values for the Aptima HSV 1 & 2 assay positive control from all valid Aptima HSV 1 & 2 assay runs performed during the clinical performance study is presented in Table 14.

**Table 14: Distribution of TTimes for Aptima HSV 1 & 2 Assay Positive Controls**

| Statistics | TTime | |
|---|---|---|
| | HSV-1 | HSV-2 |
| N | 107 | 107 |
| Mean | 20.03 | 22.01 |
| Median | 19.8 | 21.7 |
| SD | 1.198 | 1.612 |
| CV (%) | 6.0 | 7.3 |
| Minimum | 18.1 | 19.5 |
| Maximum | 22.9 | 26.2 |

CV = coefficient of variation, SD = standard deviation

## N. Instrument Name:

Panther system

## O. System Descriptions:

1. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes ____X____ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes _____ or No __X_____

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes ___X_____ or No _____

   The sponsor states there have been no changes to the Panther system software since 2014 (version 5.2.0).

   The assay software, version 2.25, originally used for the Aptima HSV 1 & 2 assay clinical studies was modified to a newer version (2.29) after the clinical reproducibility testing was completed. The modified assay software version 2.29 uses the same parameters as are planned to be used in the version for commercial use. Data generated

from the Aptima HSV 1 & 2 assay clinical testing sites were reprocessed using the new assay software version 2.29. Hologic reprocessed the data using a validated tool, which processes results in the same manner as the Panther system to demonstrate comparability between software versions.

3. Specimen Identification:

   Patient ID/Sample ID is is labeled with a unique barcode, which is tracked by the software to prevent re-use and track positive sample identification.

4. Specimen Sampling and Handling:

   Not Applicable

5. Calibration:

   Real Time Fluorometers (RTF) undergo a single calibration during manufacturing. No additional calibration is performed by the end user.

6. Quality Control:

   The internal control IC) consists of a random sequence of RNA unrelated to HSV and is introduced to each reaction during sample preparation. The IC is amplified in the same reaction as the HSV-1 and HSV-2 mRNA targets. It is used to determine the validity of each individual reaction and as an indicator of capture, amplification and/or detection inhibition, and detection step errors, as well as to control for operator and instrument errors.

   Two controls are provided by Hologic to the user in the Aptima HSV Controls Kit: one HSV dual positive control and one negative control. The positive control is composed of HSV-1 and HSV-2 in-vitro transcript (IVT) at known concentrations. These controls must generate results within predefined specifications to be valid. The negative control is composed of a buffered solution and must also provide a valid negative result for the run to be valid. Additionally, both controls must generate IC results within a predefined specification.

   A. Run Validity Criteria

   The software automatically determines run validity. The software will invalidate a run if either or both controls (negative and positive) have invalid results.

   A run may be invalidated by an operator if technical, operator, or instrument difficulties are observed and documented while performing the assay.

   An invalid run must be repeated.

B. Control Validity

Table 15 defines the TTime validity criteria for the Negative and Positive Controls.

**Table 15. TTime Validity Criteria**

| | IC TTime | HSV-1 TTime | HSV-2 TTime |
|---|---|---|---|
| **Negative Control** | ≥ 7.0 and ≤ 40.0 | - | - |
| **Positive Control** | ≥ 7.0 and ≤ 53.0 | ≥ 3.0 and ≤ 35.0 | ≥ 3.0 and ≤ 35.0 |

***Note**: External quality control samples (not provided) should be tested in conformance with local, state, and/or federal regulation or accreditation requirements and each laboratory's standard Quality Control procedures.*
***Note**: For assistance with out-of-range controls, Hologic Technical Support should be contacted.*
***Note**: When TTime cannot be calculated, a dash (-) will be displayed.*

## P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

The Panther system has been reviewed previously in K111409, K122062, P100042/S0001, P100042/S002, P120007/S0001and P120007/S002
The software documentation was reviewed and found to be acceptable. The firm provided documentation to support that the device was designed, developed, and maintained under appropriate software lifecycle processes.

## Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

## R. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.