

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION  
DECISION SUMMARY**

**A. 510(k) Number:**

K120959

**B. Purpose for Submission:**

Modification to cleared device (K090409), see section J for a description of the changes.

**C. Measurand:**

Herpes Simplex Virus (HSV-1 and HSV-2) type specific IgG antibodies to the HSV glycoprotein G (gG) 1 antigen and gG2 antigen

**D. Type of Test:**

Multiplexed micro particle immunoassay based on Luminex technology

**E. Applicant:**

Bio-Rad Laboratories

**F. Proprietary and Established Names:**

BioPlex® 2200 HSV-1 & HSV-2 IgG Kit

BioPlex® 2200 HSV-1 & HSV-2 IgG Calibrator Set

BioPlex® 2200 HSV-1 & HSV-2 IgG Control Set

**G. Regulatory Information:**

<b>Product Code</b>	<b>Classification</b>	<b>Regulation Section</b>	<b>Panel</b>
Enzyme linked immunosorbent assay, Herpes Simplex Virus, HSV-1 (MXJ)	Class II	21 CFR 866.3305, Herpes simplex virus serological assays.	Microbiology (83)
Enzyme linked immunosorbent assay, Herpes Simplex Virus, HSV-2 (MYF)	Class II	21 CFR 866.3305, Herpes simplex virus serological assays.	Microbiology (83)
Calibrator, multi-analyte mixture (JIX)	Class II	21 CFR 862.1150 – Calibrator	Clinical Chemistry (75)
Multi-analyte Controls All kinds (assayed) (JJY)	Class I	21 CFR 862.1660 –Quality control Material (Assayed and Unassayed)	Clinical Chemistry (75)

## **H. Intended Use:**

### 1. Intended use(s):

The BioPlex® 2200 HSV-1 & HSV-2 IgG kit is a multiplex flow immunoassay intended for the qualitative detection and differentiation of IgG antibodies to herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) in human serum and EDTA or heparinized plasma. The test is indicated for sexually active individuals and expectant mothers as an aid for the presumptive diagnosis of HSV-1 or HSV-2 infection. The predictive value of positive or negative results depends on the population's prevalence and the pretest likelihood of HSV-1 and HSV-2.

The test is not FDA cleared for screening blood or plasma donors. The performance of this assay has not been established for use in a pediatric population, neonates and immunocompromised patients or for use at point of care facilities.

The BioPlex 2200 HSV-1 & HSV-2 IgG kit is intended for use with the Bio-Rad BioPlex 2200 System.

#### BioPlex 2200 HSV-1 & HSV-2 IgG Calibrator Set

The BioPlex 2200 HSV-1 & HSV-2 IgG Calibrator Set is intended for the calibration of the BioPlex 2200 HSV-1 & HSV-2 IgG Reagent Pack.

#### BioPlex 2200 HSV-1 & HSV-2 IgG Control Set

The BioPlex 2200 HSV-1 & HSV-2 IgG Control Set is intended for use as an assayed quality control to monitor the overall performance of the BioPlex 2200 Instrument and BioPlex HSV-1 & HSV-2 IgG Reagent Pack in the clinical laboratory. The performance of the BioPlex 2200 HSV-1 & HSV-2 IgG Control Set has not been established with any other HSV-1 and HSV-2 antibody assays.

2. Indication(s) for use:

Same as Intended Use

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

Bio-Rad BioPlex 2200 System

**I. Device Description:**

The BioPlex 2200 HSV-1 & HSV-2 IgG kit is a multiplexed micro particle bead based immunoassay for the qualitative detection of IgG antibodies to HSV glycoprotein G (gG) 1 and 2 in human serum and EDTA or heparinized plasma using the Luminex flow cytometry technology. The BioPlex 2200 HSV-1 & HSV-2 IgG Calibrators set consists of four (4) distinct serum based calibrators. The BioPlex 2200 HSV-1 & HSV-2 IgG Control set consists of 2 vials of the BioPlex 2200 HSV-1 & HSV-2 IgG Positive Control and 2 vials of the BioPlex 2200 HSV-1 & HSV-2 IgG Negative Control. The positive controls are provided in a human serum matrix made from defibrinated plasma with added antibodies to HSV-1 and HSV-2 derived from human disease state plasma. The negative controls are provided in a human serum matrix made from defibrinated plasma.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):

BioPlex 2200 HSV 1 & 2 Kit

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

K090409

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	The BioPlex <sup>®</sup> 2200 HSV-1 &	same

<b>Similarities</b>		
Item	Device	Predicate
	<p>HSV-2 IgG kit is a multiplex flow immunoassay intended for the qualitative detection and differentiation of IgG antibodies to herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) in human serum and EDTA or heparinized plasma. The test is indicated for sexually active individuals and expectant mothers as an aid for the presumptive diagnosis of HSV-1 or HSV-2 infection. The predictive value of positive or negative results depends on the population's prevalence and the pretest likelihood of HSV-1 and HSV-2.</p> <p>The test is not FDA cleared for screening blood or plasma donors. The performance of this assay has not been established for use in a pediatric population, neonates and immunocompromised patients or for use at point of care facilities.</p> <p>The BioPlex 2200 HSV-1 &amp; HSV-2 IgG kit is intended for use with the Bio-Rad BioPlex 2200 System..</p>	
Matrix	Serum and EDTA or heparinized plasma.	same
Antigen	<ol style="list-style-type: none"> <li>1. Recombinant gG1 antigen (molecular weight 55 KD)</li> <li>2. Recombinant gG2 antigen (molecular weight 31 KD)</li> </ol>	same
Technology	Multiplexed microparticle flow cytometry immunoassay	same

Differences		
Item	Device	Predicate
QC procedure	QC once per day and per new reagent pack lot	QC once per pack and per day
Bead Reagent	2 mg/mL protein stabilizer (bovine) and protease inhibitor in particle (bead) diluent	1 mg/mL protein stabilizer (bovine)

**K. Standard/Guidance Document Referenced (if applicable):**

1. CLSI EP05-A2 - Evaluation of precision performance of quantitative measurement methods
2. CLSI EP07-A2 - Interference testing in clinical chemistry
3. CLSI EP09-A2 - Method comparison and bias estimation using patient samples (This is used for Matrix Comparison studies)
4. CLSI EP12-A2- User protocol for evaluation of qualitative test performance
5. EN 1360:200 - Stability testing of In Vitro Diagnostic Reagents

**L. Test Principle:**

The BioPlex 2200 HSV-1 & HSV-2 IgG kit is an automated system, it uses the following procedure.

The kit contains two different populations of dyed beads are each coated with HSV 1 & 2 gG1 and gG2 antigens. The BioPlex 2200 System combines an aliquot of patient sample, sample diluent, and bead set reagent into a reaction vessel. The mixture is incubated at 37°C. After a wash cycle, anti-human IgG antibody, conjugated to phycoerythrin (PE), is added to the dyed beads and this mixture is incubated at 37°C. The excess conjugate is removed in another wash cycle, and the beads are resuspended in wash buffer. The bead mixture then passes through the detector. The identity of the dyed beads is determined by the fluorescence of the dyes, and the amount of antibody captured by the antigen is determined by the fluorescence of the attached PE. Raw data is calculated in relative fluorescence intensity (RFI).

Three additional dyed beads, an Internal Standard Bead (ISB), a Serum Verification Bead (SVB) and a Reagent Blank Bead (RBB) are present in each reaction mixture to verify detector response, the addition of serum to the reaction vessel and the absence of significant non-specific binding in serum.

The instrument is calibrated using a set of four (4) distinct calibrator vials, supplied

separately by Bio-Rad Laboratories. The 4 vials representing 4 different antibody concentrations are used for calibration. The result for each of these antibodies is expressed as an antibody index (AI).

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

1. Analytical performance:

*a. Precision/Reproducibility:*

A precision panel, consisting of 8 serum panel members for each analyte, was prepared by Bio-Rad Laboratories. For each analyte, 2 had high positive, 2 had low positive, 2 had antibody levels near the cutoff, and 2 high negative panel members.

Precision testing was performed at Bio-Rad Laboratories on one lot of the modified BioPlex 2200 HSV-1 & HSV-2 IgG kit. Each of the 8 panel members was tested in duplicate on 2 runs per days for 5 days in a total of 20 results per panel member (2 replicates x 2 runs x 5 days = 20 replicates per panel member). The data were analyzed for intra-assay and inter-assay precision in accordance to the CLSI EP5-A2 guideline. The standard deviation (SD) and percent coefficient of variation (%CV) were calculated. The results of the precision testing and comparison between the modified device and the cleared device are shown below. The results demonstrate that the performance of the modified device is substantially equivalent to the cleared device. For the precision and reproducibility information of the BioPlex 2200 HSV-1 & HSV-2 IgG kit please refer to the decision summary of K090409.

**HSV-1 IgG Precision Comparison Summary: Modified vs. Predicate devices**

HSV-1 IgG Panel Members	Mean, AI		Within Run %CV		Total Precision %CV		Between Run %CV		Between Day %CV	
	Predicate	Modified	Predicate	Modified	Predicate	Modified	Predicate	Modified	Predicate	Modified
High Negative	0.5	0.5	6.3%	4.5%	6.3%	4.5%	0.0%	0.0%	0.0%	0.0%
High Negative	0.7	0.7	6.4%	5.5%	7.6%	7.8%	0.0%	5.5%	4.1%	0.0%
Near Cutoff	1.0	1.0	7.1%	5.9%	7.7%	8.4%	3.2%	5.9%	0.0%	0.0%
Near Cutoff	1.0	1.0	5.0%	5.0%	6.9%	5.0%	3.2%	0.0%	3.5%	0.0%
Low Positive	1.3	1.3	6.9%	4.9%	8.6%	6.2%	3.0%	3.8%	4.3%	0.0%
Low Positive	1.7	1.6	8.0%	8.0%	10.1%	10.3%	6.0%	3.1%	1.0%	5.6%
High Positive	3.2	3.1	4.1%	5.4%	4.3%	6.0%	1.2%	0.0%	0.0%	2.6%
High Positive	3.6	3.4	6.0%	6.4%	6.4%	7.6%	2.2%	0.0%	0.0%	4.1%

**HSV-2 IgG Precision Comparison Summary: Modified vs. Predicate devices**

HSV-2 IgG Panel Members	Mean, AI		Within Run %CV		Total Precision %CV		Between Run %CV		Between Day %CV	
	Predicate	Modified	Predicate	Modified	Predicate	Modified	Predicate	Modified	Predicate	Modified
High Negative	0.7	0.6	6.4%	6.5%	7.8%	6.5%	4.5%	0.0%	0.0%	0.0%
High Negative	0.8	0.8	6.3%	5.6%	7.4%	7.4%	4.0%	4.8%	0.0%	0.0%
Near Cutoff	1.1	1.1	4.1%	5.4%	5.2%	6.3%	2.0%	2.9%	2.6%	1.6%
Near Cutoff	1.2	1.1	4.9%	5.0%	4.9%	5.0%	0.0%	0.0%	0.0%	0.0%

Low Positive	1.3	1.3	7.7%	4.6%	9.8%	5.2%	2.4%	2.4%	5.6%	0.6%
Low Positive	2.4	2.3	6.3%	5.8%	6.8%	6.7%	2.6%	3.4%	0.0%	0.0%
High Positive	4.4	4.1	6.1%	5.2%	6.1%	6.4%	0.0%	1.7%	0.0%	3.3%
High Negative	4.8	4.7	3.7%	3.5%	3.7%	4.1%	0.0%	1.7%	0.0%	1.1%

*b. Linearity/assay reportable range:*

Not applicable

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

Not applicable

*d. Detection limit:*

Not applicable

*e. Analytical specificity:*

Testing for interfering substances was conducted according to CLSI EP7-A2. Samples were prepared by blending a pool of negative human serum with samples positive to HSV-1 and HSV-2 IgG to achieve values of 2.0 to 3.0 AI and interferent or solvent (negative control) was added exogenously at levels indicated below. Test and control samples were evaluated in replicates of ten using the modified BioPlex 2200 HSV-1 & HSV-2 IgG Kits. The results demonstrated equivalence with the original (predicate) device. The percent change in signal ranged from -5.0 to 10.0% and -9.1% to 9.5% for the predicate and modified HSV-1 IgG assays respectively and -4.0 to 8.0% and -4.0% to 7.7% for the predicate and modified HSV-2 IgG assays. For the additional interference information for the BioPlex 2200 HSV-1 & HSV-2 IgG kit please refer to the decision summary for K090409.

**Interference Substances**

<b>Substance</b>	<b>Concentration</b>
Hemoglobin	500 mg/dL
Bilirubin (unconjugated)	20 mg/dL
Bilirubin (conjugated)	30 mg/dL
Cholesterol	500 mg/dL
Red Blood Cells	0.4% (v/v)
Gamma-Globulin	6 g/dL
Triglycerides	3300 mg/dL
Total Protein (albumin)	12 g/dL

<b>Substance</b>	<b>Concentration</b>
Beta-Carotene	0.6 mg/dL
Ascorbic Acid	3 mg/dL
Lithium Heparin	8000 units/dL
Sodium Heparin	8000 units/dL
EDTA	800 mg/dL
Sodium Citrate	1000 mg/dL

*f. Assay cut-off:*

The assay cut-off remains unchanged and the precision around the cut-off is equivalent to the original device (see K090409).

2. Comparison studies:

*a. Method comparison with predicate device:*

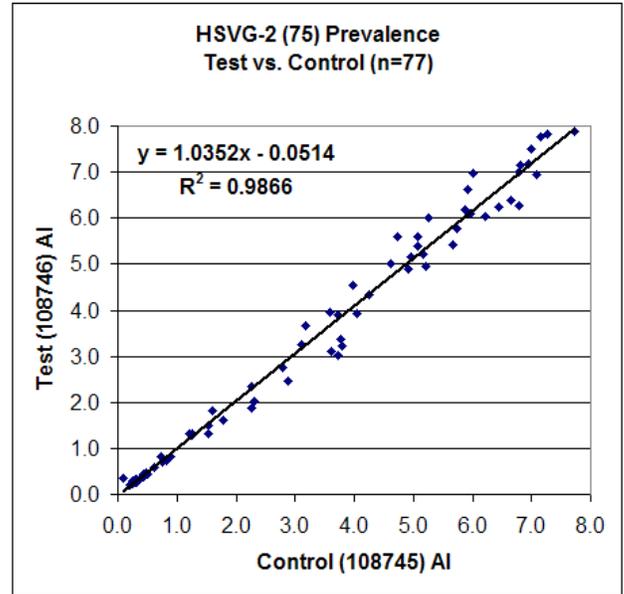
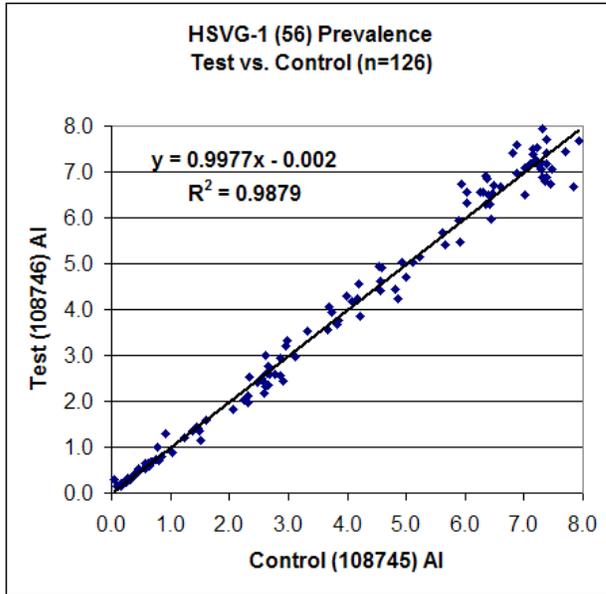
Performance of the modified BioPlex HSV-1 & HSV-2 IgG kit was tested against the cleared BioPlex HSV-1 & HSV-2 IgG Kit using samples prospectively collected from sexually active individuals where HSV-1 and HSV-2 tests were ordered. The comparative performance was also evaluated using the CDC HSV reference serum sample panel (N=80). The results of this analysis are presented below and the conclusion of the assessment is that the performance of the device remains unchanged. For the sensitivity and specificity of the BioPlex HSV-1 & HSV-2 IgG kit versus the reference method please refer to the K090409 package insert.

a. Sexually Active Individuals – HSV-1 and HSV-2 Test Ordered

Method comparison was conducted following EP09. Linear regression analysis was performed using the results within the measuring range to compare the modified and predicate assays. The regression parameters (slope, intercept, and correlation ( $R^2$ )) and scatter plots of the modified device versus the cleared device are presented below.

Statistics of regression analysis

BioPlex Assay	Slope	Intercept	Correlation ( $R^2$ )
HSV-1	0.9977	-0.002	0.9879
HSV-2	1.0352	-0.0514	0.9866



Sexually Active Individuals With an HSV-1 Test Ordered:  
Modified BioPlex 2200 HSV-1 IgG versus Cleared BioPlex 2200 HSV-1 IgG

		Predicate(BioPlex 2200 HSV-1 IgG results)				
		Positive	Equivocal	Negative	Total	% Agreement
BioPlex 2200 HSV-1 IgG	Positive	280	1	0	281	PPA=100%(280/280), 95% CI 98.6-100%
	Equivocal	0	1	1	2	
	Negative	0	0	116	116	NPA=98.3%(116/118), 95% CI 98.2-99.9%
	Total	280	2	117	399	

Sexually Active Individuals With an HSV-2 Test Ordered:  
Modified BioPlex 2200 HSV-2 IgG versus cleared BioPlex 2200 HSV-1 IgG

		Predicate(BioPlex 2200 HSV-2 IgG results)				
		Positive	Equivocal	Negative	Total	% Agreement
BioPlex 2200 HSV-2 IgG	Positive	166	0	0	166	PPA=99.4%(166/167), 95%CI 96.7-99.9%
	Equivocal	0	0	0	0	
	Negative	0	1	232	233	NPA=100%(232/232), 95% CI 98.6-100%
	Total	166	1	232	399	

*Agreement with CDC Panel*

The purpose of this study is to demonstrate that the test results of CDC HSV-1 and HSV-2 IgG Panel between the current marketed device (Predicate, K090409) and the modified device are equivalent for the BioPlex 2200 HSV-1 & HSV-2 IgG assay. Testing was conducted internally at Bio-Rad Laboratories. The testing was performed using the masked, well characterized HSV serum panel from the CDC. The panel consists of 24% HSV-1 and HSV-2 dual-positive samples, 50% HSV-1 positive and 50% HSV-1 negative samples and 48% HSV-2 positive and 52% HSV-2 negative samples. The results are presented to convey further information on the performance of the test kit and do not imply endorsement of the assay by the CDC. Results are shown below.

		CDC panel HSV-1 IgG results			
BioPlex 2200 HSV-1 IgG Result		Positive	Negative	Total	% Agreement
	Positive	42	0	42	PPA: 100% (42/42) 95% CI= 91.6-100%
	Equivocal	0	1	1	0
	Negative	0	37	37	NPA: 97.4% (37/38) 95% CI= 86.5-99.5%
	Total	42	38	80	

		CDC panel HSV-2 IgG Results			
BioPlex 2200 HSV-2 IgG Results		Positive	Negative	Total	% Agreement
	Positive	40	0	40	PPA: 100% (40/40) 95% CI 91.2-100%
	Equivocal	0	0	0	
	Negative	0	40	40	PPA: 100% (40/40) 95% CI 91.2-100%
	Total	40	40	80	

*b. Matrix comparison:*

Matched serum and plasma (EDTA and heparin sodium) samples drawn from the same donor were acquired from commercial sources. For each assay in the panel more than 40 samples were collected within the measurement range of the assay. Samples were assayed in replicates of two using the modified BioPlex 2200 HSV-1 & HSV-2 IgG kits. Plasma AI values were compared to matched serum AI values. The regression correlation parameters for the slopes, intercepts, and correlation coefficient (r) are shown below.

Matrix Comparison

<b>BioPlex Assay</b>	<b>Matrix</b>	<b>N</b>	<b>Slope</b>	<b>Intercept</b>	<b>Correlation (r)</b>
HSV-1	EDTA vs. Serum	47	1.0023	-0.0358	0.9902
HSV-1	Heparin vs. Serum	47	0.9988	-0.0069	0.9946
HSV-2	EDTA vs. Serum	44	0.9945	-0.0737	0.9945
HSV-2	Heparin vs. Serum	44	0.9523	-0.0649	0.9946

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):

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The observed prevalence and expected values for the modified BioPlex 2200 HSV-1 & HSV-2 IgG kit are presented in the tables below by age and gender for serum samples from sexually active individuals where an HSV-1 (N=200) and HSV-2 (N=200) tests were ordered. The testing was performed internally at the manufacturing site and the results of the modified device were equivalent to those of the original cleared device. For the BioPlex 2200 HSV-1 & HSV-2 IgG kit cleared expected values and positive and negative predictive values for the intended use populations please refer to the decision summary of K090409.

Sexually Active Individuals with an HSV-1 Test Ordered (N=200):  
Modified BioPlex 2200 HSV-1 IgG

<b>BioPlex 2200 HSV-1 IgG</b>								
<b>Age in Years</b>	<b>Gender</b>	<b>Positive</b>		<b>Equivocal</b>		<b>Negative</b>		<b>Total</b>
		<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>
<b>18-20</b>	<b>F</b>	4	80.0%	0	0.0%	1	20.0%	5
	<b>M</b>	6	60.0%	0	0.0%	4	40.0%	10
<b>21-30</b>	<b>F</b>	10	55.6%	0	0.0%	8	44.4%	18
	<b>M</b>	13	61.9%	0	0.0%	8	38.1%	21
<b>31-40</b>	<b>F</b>	17	94.4%	0	0.0%	1	5.6%	18
	<b>M</b>	15	75.0%	0	0.0%	5	25.0%	20
<b>41-50</b>	<b>F</b>	12	92.3%	0	0.0%	1	7.7%	13
	<b>M</b>	23	71.9%	0	0.0%	9	28.1%	32
<b>51-60</b>	<b>F</b>	8	72.7%	0	0.0%	3	27.3%	11
	<b>M</b>	16	72.7%	1	4.5%	5	22.7%	22
<b>61-70</b>	<b>F</b>	8	61.5%	0	0.0%	5	38.5%	13
	<b>M</b>	9	75.0%	0	0.0%	3	25.0%	12
<b>71-80</b>	<b>F</b>	0	0.0%	0	0.0%	1	100.0%	1
	<b>M</b>	2	100.0%	0	0.0%	0	0.0%	2
<b>81-90</b>	<b>F</b>	0	0.0%	0	0.0%	0	0.0%	0
	<b>M</b>	0	0.0%	0	0.0%	0	0.0%	0
<b>Unknown</b>	<b>Unknown</b>	1	50.0%	0	0.0%	1	50.0%	2
<b>Total</b>		144	72.0%	1	0.5%	55	27.5%	200

Sexually Active Individuals with an HSV-2 Test Ordered (N=200):  
Modified BioPlex 2200 HSV-2 IgG

<b>BioPlex 2200 HSV-2 IgG</b>								
<b>Age in Years</b>	<b>Gender</b>	<b>Positive</b>		<b>Equivocal</b>		<b>Negative</b>		<b>Total</b>
		<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>
<b>18-20</b>	<b>F</b>	2	66.7%	0	0.0%	1	33.3%	3
	<b>M</b>	1	16.7%	0	0.0%	5	83.3%	6
<b>21-30</b>	<b>F</b>	5	26.3%	0	0.0%	14	73.7%	19
	<b>M</b>	13	38.2%	0	0.0%	21	61.8%	34
<b>31-40</b>	<b>F</b>	7	77.8%	0	0.0%	2	22.2%	9
	<b>M</b>	9	29.0%	0	0.0%	22	71.0%	31
<b>41-50</b>	<b>F</b>	6	66.7%	0	0.0%	3	33.3%	9
	<b>M</b>	15	42.9%	0	0.0%	20	57.1%	35
<b>51-60</b>	<b>F</b>	6	66.7%	0	0.0%	3	33.3%	9
	<b>M</b>	6	37.5%	0	0.0%	10	62.5%	16
<b>61-70</b>	<b>F</b>	4	50.0%	0	0.0%	4	50.0%	8
	<b>M</b>	3	20.0%	0	0.0%	12	80.0%	15
<b>71-80</b>	<b>F</b>	0	0.0%	0	0.0%	0	0.0%	0
	<b>M</b>	0	0.0%	0	0.0%	2	100.0%	2
<b>81-90</b>	<b>F</b>	0	0.0%	0	0.0%	1	100.0%	1
	<b>M</b>	0	0.0%	0	0.0%	0	0.0%	0

<b>Unknown</b>	<b>Unknown</b>	1	33.3%	0	0.0%	2	66.7%	3
<b>Total</b>		78	39.0%	0	0.0%	122	61.0%	200

**N. Proposed Labeling:**

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

**O. Conclusion:**

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