BioPlex® 2200 EBV IgM 510(k) Summary

NOV 2 2012

Bio-Rad Laboratories hereby submits this 510(k) in accordance with the requirements of SMDA 1990 and 21 CFR 807.92. This summary of 510(k) safety and effectiveness information provides detail as a basis for a determination of substantial equivalence for the BioPlex® 2200 EBV IgM kit.

510(k) Number:

K123021

Summary Preparation Date:

October 30, 2012

Applicant:

Bio-Rad Laboratories

Contact:

Juang Wang
Regulatory Affairs Representative

Purpose for Submission:

Modification to cleared device (K062213), see section Substantial Equivalence Information for a description of the changes.

Measurand:

Epstein-Barr Virus Viral Capsid Antigen (EBV VCA) IgM antibodies to VCA glycoprotein (GP125/p18) and Heterophile antibodies

Type of Test:

Multiplexed micro particle immunoassay based on Luminex technology

Proprietary and Established Names:

BioPlex® 2200 EBV IgM Kit

BioPlex® 2200 EBV IgM Calibrator Set

BioPlex® 2200 EBV IgM Control Set

Regulatory Information:

Product Code	Classification	Regulation Section	Panel
Antibody IgM, if, Epstein-Barr virus (LJN)	Class I	21 CFR § 866.3235, Epstein-Barr virus serological reagents	Microbiology (83)
System, Test, Infectious Mononucleosis (KTN)	Class II	21 CFR § 866.5640, Infectious mononucleosis immunological test system	Immunology (82)
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)

Intended Use:

1. Intended use(s):

   The BioPlex® 2200 EBV IgM kit is a multiplex flow immunoassay intended for the qualitative detection of two (2) separate analytes; Epstein-Barr Virus Viral Capsid Antigen (EBV VCA) IgM antibodies and Heterophile antibodies in human serum. The test system can be used in conjunction with the BioPlex® 2200 EBV IgG kit as an aid in the laboratory diagnosis of infectious mononucleosis (IM).

   The BioPlex® 2200 EBV IgM kit is intended for use with the Bio-Rad BioPlex® 2200 System.

   Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients, cord blood, neonatal specimens, or infants. Assay performance characteristics have not been established for the diagnosis of nasopharyngeal carcinoma, Burkitt's lymphoma, and other EBV-associated lymphomas.

   BioPlex® 2200 EBV IgM Calibrator Set

   The BioPlex® 2200 EBV IgM Calibrator Set is intended for the calibration of the BioPlex® 2200 EBV IgM Reagent Pack.

   BioPlex® 2200 EBV IgM Control Set

   The BioPlex® 2200 EBV IgM Control Set is intended for use as an assayed quality control to monitor the overall performance of the BioPlex® 2200 Instrument and BioPlex® EBV IgM Reagent Pack in the clinical laboratory. The performance of the BioPlex® EBV IgM Control Set has not been established with any other EBV IgM 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

Device Description:

The BioPlex 2200 EBV IgM kit is a multiplexed micro particle bead based immunoassay for the qualitative detection of IgM antibodies to EBV VCA GP125/p18 and Heterophile antigen in human serum using the Luminex flow cytometry technology. The BioPlex 2200 EBV IgM Calibrators set consists of two (2) distinct serum based calibrators. The BioPlex 2200 EBV IgM Control set consists of 2 vials of the BioPlex 2200 EBV IgM Positive Control and 2 vials of the BioPlex 2200 EBV IgM Negative Control. The positive controls are provided in a human serum matrix made from defibrinated plasma with added antibodies to EBV VCA GP125/p18 and Heterophile antigen derived from human disease state plasma. The negative controls are provided in a human serum matrix made from defibrinated plasma.

Substantial Equivalence Information:

1. Predicate device name(s):
   BioPlex 2200 EBV IgM Kit

2. Predicate 510(k) number(s):
   K062213

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	The BioPlex® 2200 EBV IgM kit is a multiplex flow immunoassay intended for the qualitative detection of two (2) separate analytes; Epstein-Barr Virus Viral Capsid Antigen (EBV VCA) IgM antibodies and Heterophile antibodies in human serum. The test system can be used in conjunction with the BioPlex® 2200 EBV IgG kit as an aid in the laboratory diagnosis of infectious mononucleosis (IM).	same

Similarities		
Item	Device	Predicate
	The BioPlex 2200 EBV IgM kit is intended for use with the Bio-Rad BioPlex 2200 System Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients, cord blood, neonatal specimens, or infants. Assay performance characteristics have not been established for the diagnosis of nasopharyngeal carcinoma, Burkitt's lymphoma, and other EBV-associated lymphomas.	
Matrix	Serum	same
Antigen	Recombinant protein to EBV VCA GP125/p18 (40kD), and Heterophile antigen (horse erythrocyte stromal extract)	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 (goat) and protease inhibitor in particle (bead) diluent	None
Software Version	Version 2.2/4.0	Version 1.1/1.2

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 Method 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

Test Principle:

The BioPlex 2200 EBV IgM kit is an automated system and uses the following procedure.

The kit contains two different populations of dyed beads; one population is coated with EBV VCA glycoprotein (GP125/p18) and the other is coated with Heterophile antigens. The BioPlex 2200 System combines an aliquot of patient sample, sample diluent, and bead reagent into a reaction vessel. The mixture is incubated at 37°C. After a wash cycle, anti-human IgM 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 two (2) distinct calibrator vials, supplied separately by Bio-Rad Laboratories. The two (2) vials representing two (2) different antibody concentrations are used for calibration. The result for each of these antibodies is expressed as an antibody index (AI).

Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*
   A precision panel, consisting of nine (9) serum panel members for each analyte, was prepared by Bio-Rad Laboratories. For each analyte, two (2) panel members were high positive (2.5 to 4.0 AI), three (3) were low positive (1.4 to 2.0 AI), two (2) had antibody levels near the cutoff (0.7 to 1.3 AI), and two (2) were high negative (0.2 to 0.6 AI).

   Precision testing was performed at Bio-Rad Laboratories on one lot of the

modified BioPlex 2200 EBV IgM kit. Each of the nine (9) panel members was tested in duplicate on two (2) runs per days for ten (10) days for a total of 40 results per panel member (2 replicates x 2 runs x 10 days = 40 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 EBV IgM kit please refer to the decision summary of K062213.

VCA IgM Precision Comparison Summary: Modified vs. Predicate devices

VCA IgM	Mean (AI)		Within Run %CV		Between Run %CV		Between Day %CV		Total Precision %CV	
Panel Members	Predicate	Modified	Predicate	Modified	Predicate	Modified	Predicate	Modified	Predicate	Modified
High Negative	0.4	0.4	8.8%	5.6%	0.0%	0.0%	2.9%	0.0%	9.3%	5.6%
High Negative	0.5	0.5	8.4%	7.7%	3.2%	0.0%	0.0%	4.6%	8.9%	9.0%
Near Cutoff	0.9	0.9	4.3%	6.1%	3.0%	0.0%	0.0%	2.1%	5.3%	6.4%
Near Cutoff	1.2	1.1	4.4%	7.7%	2.6%	0.0%	2.9%	0.0%	5.9%	7.7%
Low Positive	1.5	1.3	4.9%	4.7%	0.0%	0.0%	2.3%	1.9%	5.4%	5.1%
Low Positive	1.9	1.6	7.0%	7.4%	2.4%	3.3%	0.0%	0.0%	7.3%	8.1%
Low Positive	2.1	1.9	5.3%	6.6%	1.3%	2.2%	1.9%	3.1%	5.8%	7.6%
High Positive	3.2	2.9	4.4%	4.5%	0.0%	0.5%	1.2%	0.0%	4.5%	4.5%
High Positive	3.8	3.8	2.3%	2.2%	2.0%	1.6%	0.6%	0.0%	3.1%	2.7%

Heterophile IgM Precision Comparison Summary: Modified vs. Predicate devices

Heterophile IgM	Mean (AI)		Within Run %CV		Between Run %CV		Between Day %CV		Total Precision %CV	
Panel Members	Predicate	Modified	Predicate	Modified	Predicate	Modified	Predicate	Modified	Predicate	Modified
High Negative	0.6	0.6	5.3%	6.5%	0.0%	0.0%	0.0%	4.5%	5.3%	7.9%
High Negative	0.6	0.6	6.5%	7.0%	0.0%	0.0%	4.4%	4.7%	7.8%	8.4%
Near Cutoff	0.8	0.8	5.6%	6.8%	2.0%	0.0%	2.5%	1.8%	6.4%	7.1%
Near Cutoff	0.8	0.8	5.6%	5.6%	4.0%	0.0%	0.0%	4.2%	6.8%	7.0%
Low Positive	1.6	1.6	3.8%	4.9%	3.8%	0.0%	0.0%	2.1%	5.4%	5.4%
Low Positive	1.6	1.6	4.3%	5.3%	0.0%	0.0%	2.5%	2.8%	5.0%	6.0%
Low Positive	2.3	2.2	4.9%	5.2%	1.0%	1.8%	0.0%	2.1%	5.0%	5.9%
High Positive	2.7	2.6	3.1%	4.1%	1.2%	2.4%	1.4%	2.3%	3.6%	5.3%
High Negative	3.1	3.0	3.5%	4.6%	2.7%	0.0%	0.0%	2.1%	4.4%	5.1%

b. *Linearity/assay reportable range:*
Not applicable

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
No formulation changes have been made to the controls and calibrators. The control and calibrators are traceable against frozen internal standards which are anchored to the quantitation panel. The quantitation panel consists of patient samples whose analyte values span the assay range. The performance of the accelerated studies concluded that the modified EBV IgM reagent kit is equivalent to the current kit as all specifications were met.

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 for EBV VCA IgM and Heterophile IgM to achieve values of 2.0 to 3.0 AI and interferent or solvent (negative control) was added exogenously at the levels indicated in the table below. Test (containing interferent) and control samples were evaluated in replicates of ten using the modified BioPlex 2200 EBV IgM kit. The results demonstrated equivalence with the original (predicate) device. The percent change in signal ranged from -5.6% to 5.6% and -10.0% to 0.0% for the predicate and modified EBV VCA IgM assays, respectively, and -7.4% to 4.2% and -11.1% to 7.4% for the predicate and modified Heterophile IgM assays, respectively. For information on testing for interfering substances with the predicate BioPlex 2200 EBV IgM kit please refer to the decision summary for K062213.

Interference Substances

Substance	**Concentration**
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
Beta-Carotene	0.6 mg/dL
Ascorbic Acid	3 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 K062213).

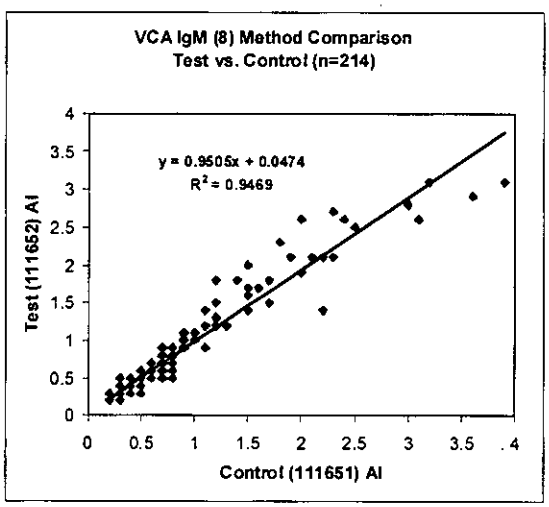
2. Comparison studies:

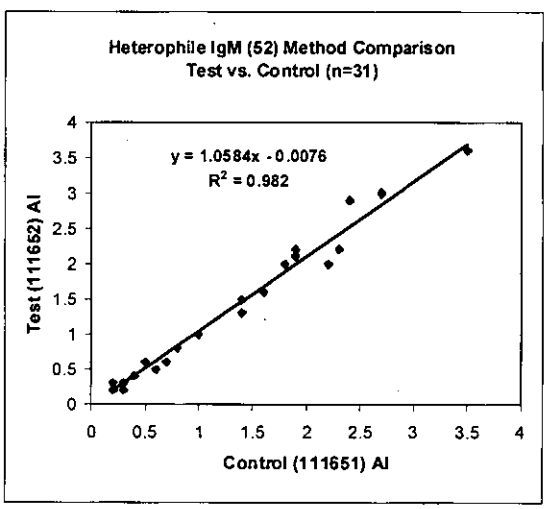
   a. *Method comparison with predicate device:*
   Performance of the modified BioPlex 2200 EBV IgM kit was tested against the cleared (predicate) BioPlex 2200 EBV IgM Kit using samples prospectively collected from individuals where an EBV IgM test was ordered (N=622). The results of this analysis are presented below and the conclusion of the assessment is that the performance of the device remains unchanged. For the assay performance of the BioPlex EBV IgM kit versus other commercially available IgM EIA kits please refer to K062213.

   Prospectively Collected Samples
   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 predicate device are presented below.

   Statistics of regression analysis

BioPlex EBV IgM Assay	Slope	Intercept	Correlation (R^2)
VCA IgM	0.9505	0.0474	0.9469
Heterophile IgM	1.0584	-0.0076	0.9820





Individuals With a VCA IgM Test Ordered:
Modified BioPlex 2200 EBV IgM versus Cleared BioPlex 2200 EBV IgM

		Predicate(BioPlex 2200 VCA IgM results)				
Modified BioPlex 2200 VCA IgM		Positive	Equivocal	Negative	Total	%Agreement
	Positive	78	5	0	83	PPA=98.7%(78/79), 95% CI 93.2-99.8%
	Equivocal	1	8	2	11	

	Negative	0	0	528	528	NPA=98.7%(528/535), 95% CI 97.3-99.4%
	Total	79	13	530	622	

Individuals With a Heterophile IgM Test Ordered:
Modified BioPlex 2200 EBV IgM versus cleared BioPlex 2200 EBV IgM

		Predicate(BioPlex 2200 Heterophile IgM results)				
Modified BioPlex 2200 Heterophile IgM		Positive	Equivocal	Negative	Total	%Agreement
	Positive	28	0	0	28	PPA=100%(28/28), 95%CI 87.9-100%
	Equivocal	0	1	0	1	
	Negative	0	0	593	593	NPA=100%(593/593), 95% CI 99.4-100%
	Total	28	1	593	622	

Retrospective Positive Samples

The purpose of this study was to demonstrate that the test results of retrospective positive samples between the current marketed device (Predicate, K062213) and the modified device are equivalent for the BioPlex 2200 EBV IgM assay. The testing was performed using the samples from individuals who were presumptively positive for either VCA IgM or Heterophile IgM. Results are shown below.

		Predicate(BioPlex 2200 VCA IgM results)				
BioPlex 2200 VCA IgM		Positive	Equivocal	Negative	Total	%Agreement
	Positive	81	0	0	81	PPA=100%(81/81), 95% CI 95.5 -100%
	Equivocal	0	0	0	0	
	Negative	0	0	0	0	NPA=N/A
	Total	81	0	0	81	

		Predicate(BioPlex 2200 Heterophile IgM results)				
BioPlex 2200 Heterophile IgM		Positive	Equivocal	Negative	Total	%Agreement
	Positive	81	0	0	81	PPA=100%(81/81), 95% CI 95.5 -100%
	Equivocal	0	0	0	0	
	Negative	0	0	0	0	NPA=N/A
	Total	81	0	0	81	

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):

   Refer to Method Comparison

4. Clinical cut-off:
   Refer to K062213

5. Expected values/Reference range:
   The observed expected values for the modified BioPlex 2200 EBV IgM kit are presented in the tables below by age and gender for serum samples from individuals where EBV (N=622) and Heterophile (N=622) tests were ordered. The results from the modified device were equivalent to those from the predicate device. For the expected values and positive and negative predictive values for the intended use populations obtained previously with the predicate BioPlex 2200 EBV IgM kit, please refer to the decision summary of K062213.

   Individuals with a VCA IgM Test Ordered (N=622):
   Modified BioPlex 2200 VCA IgM

Modified BioPlex 2200 VCA IgM								
Age in Years	**Gender**	**Positive**		**Equivocal**		**Negative**		**Total**
		N	**%**	**N**	**%**	**N**	**%**	**N**
<5	F	3	10.0%	0	0.0%	27	90.0%	30
	M	5	15.2%	1	3.0%	27	81.8%	33
5-12	F	7	11.1%	3	4.8%	53	84.1%	63
	M	5	7.9%	2	3.2%	56	88.9%	63
13-20	F	18	21.4%	2	2.4%	64	76.2%	84
	M	10	25.0%	0	0.0%	30	75.0%	40
21-30	F	6	13.3%	0	0.0%	39	86.7%	45
	M	6	18.8%	1	3.1%	25	78.1%	32
31-40	F	6	11.5%	1	1.9%	45	86.5%	52
	M	1	4.2%	0	0.0%	23	95.8%	24
41-50	F	4	11.8%	0	0.0%	30	88.2%	34
	M	3	10.7%	0	0.0%	25	89.3%	28
51-60	F	4	16.0%	0	0.0%	21	84.0%	25

	M	3	11.1%	0	0.0%	24	88.9%	27
61-70	F	1	7.7%	0	0.0%	12	92.3%	13
	M	1	5.0%	1	5.0%	18	90.0%	20
71-80	F	0	0.0%	0	0.0%	2	100.0%	2
	M	0	0.0%	0	0.0%	3	100.0%	3
81-90	F	0	0.0%	0	0.0%	2	100.0%	2
	M	0	0.0%	0	0.0%	2	100.0%	2
Total		83	13.3%	11	1.8%	528	84.9%	622

Individuals with a Heterophile IgM Test Ordered (N=622):
Modified BioPlex 2200 Heterophile IgM

Modified BioPlex 2200 Heterophile IgM								
Age in Years	**Gender**	**Positive**		**Equivocal**		**Negative**		**Total**
		N	**%**	**N**	**%**	**N**	**%**	**N**
<5	F	0	0.0%	0	0.0%	30	100.0%	30
	M	0	0.0%	0	0.0%	33	100.0%	33
5-12	F	3	4.8%	0	0.0%	60	95.2%	63
	M	3	4.8%	0	0.0%	60	95.2%	63
13-20	F	8	9.5%	1	1.2%	75	89.3%	84
	M	8	20.0%	0	0.0%	32	80.0%	40
21-30	F	1	2.2%	0	0.0%	44	97.8%	45
	M	3	9.4%	0	0.0%	29	90.6%	32
31-40	F	0	0.0%	0	0.0%	52	100.0%	52
	M	1	4.2%	0	0.0%	23	95.8%	24
41-50	F	0	0.0%	0	0.0%	34	100.0%	34
	M	0	0.0%	0	0.0%	28	100.0%	28
51-60	F	0	0.0%	0	0.0%	25	100.0%	25
	M	1	3.7%	0	0.0%	26	96.3%	27
61-70	F	0	0.0%	0	0.0%	13	100.0%	13
	M	0	0.0%	0	0.0%	20	100.0%	20
71-80	F	0	0.0%	0	0.0%	2	100.0%	2
	M	0	0.0%	0	0.0%	3	100.0%	3
81-90	F	0	0.0%	0	0.0%	2	100.0%	2
	M	0	0.0%	0	0.0%	2	100.0%	2
Total		28	4.5%	1	0.2%	593	95.3%	622

Individuals with a VCA IgM Test Ordered (N=622):
Predicate – k062213 BioPlex 2200 VCA IgM

K062213 BioPlex VCA IgM								
Age in Years	**Gender**	**Positive**		**Equivocal**		**Negative**		**Total**
		N	%	N	%	N	%	N
<5	F	3	10.0%	0	0.0%	27	90.0%	30
	M	4	12.1%	2	6.1%	27	81.8%	33

<5-12	F	7	11.1%	1	1.6%	55	87.3%	63
	M	6	9.5%	1	1.6%	56	88.9%	63
13-20	F	17	20.2%	3	3.6%	64	76.2%	84
	M	10	25.0%	0	0.0%	30	75.0%	40
21-30	F	5	11.1%	1	2.2%	39	86.7%	45
	M	6	18.8%	1	3.1%	25	78.1%	32
31-40	F	6	11.5%	1	1.9%	45	86.5%	52
	M	1	4.2%	0	0.0%	23	95.8%	24
41-50	F	3	8.8%	1	2.9%	30	88.2%	34
	M	3	10.7%	0	0.0%	25	89.3%	28
51-60	F	4	16.0%	0	0.0%	21	84.0%	25
	M	3	11.1%	0	0.0%	24	88.9%	27
61-70	F	1	7.7%	0	0.0%	12	92.3%	13
	M	0	0.0%	2	10.0%	18	90.0%	20
71-80	F	0	0.0%	0	0.0%	2	100.0%	2
	M	0	0.0%	0	0.0%	3	100.0%	3
81-90	F	0	0.0%	0	0.0%	2	100.0%	2
	M	0	0.0%	0	0.0%	2	100.0%	2
Total		79	12.7%	13	2.1%	530	85.2%	622

Individuals with a Heterophile IgM Test Ordered (N=622):
Predicate- k062213 BioPlex 2200 Heterophile IgM

K062213 BioPlex Heterophile IgM								
Age in Years	**Gender**	**Positive**		**Equivocal**		**Negative**		**Total**
		N	**%**	**N**	**%**	**N**	**%**	**N**
<5	**F**	0	0.0%	0	0.0%	30	100.0%	30
	M	0	0.0%	0	0.0%	33	100.0%	33
<5-12	**F**	3	4.8%	0	0.0%	60	95.2%	63
	M	3	4.8%	0	0.0%	60	95.2%	63
13-20	**F**	8	9.5%	1	1.2%	75	89.3%	84
	M	8	20.0%	0	0.0%	32	80.0%	40
21-30	**F**	1	2.2%	0	0.0%	44	97.8%	45
	M	3	9.4%	0	0.0%	29	90.6%	32
31-40	**F**	0	0.0%	0	0.0%	52	100.0%	52
	M	1	4.2%	0	0.0%	23	95.8%	24
41-50	**F**	0	0.0%	0	0.0%	34	100.0%	34
	M	0	0.0%	0	0.0%	28	100.0%	28
51-60	**F**	0	0.0%	0	0.0%	25	100.0%	25
	M	1	3.7%	0	0.0%	26	96.3%	27
61-70	**F**	0	0.0%	0	0.0%	13	100.0%	13
	M	0	0.0%	0	0.0%	20	100.0%	20
71-80	**F**	0	0.0%	0	0.0%	2	100.0%	2
	M	0	0.0%	0	0.0%	3	100.0%	3
81-90	**F**	0	0.0%	0	0.0%	2	100.0%	2
	M	0	0.0%	0	0.0%	2	100.0%	2

Total	28	4.5%	1	0.2%	593	95.3%	622

Other Supportive Device and Instrument Information:

1. Design Control Activities Summary
   This analysis was provided to support the labeling modification change. See Substantial Equivalence Information for a description of the changes.

   a. *Risk Analysis:*
   A Failure Mode and Effect Analysis (FMEA) method was used to facilitate, capture, and quantify the potential impacts of a low signal pack (LSP) occurrence. The LSP was a phenomenon where a low frequency of BioPlex 2200 assays (1-2%) experienced a signal depression for specific analytes within the packs. The FMEA analysis determined the severity of consequences of failure for each of the assays taking into consideration the guidance documents; CFR Part 860, ISO: 14971 (2009) Annex H and IVDD (98/79/EC). Additionally, the potential misuse or off-label use of the assay was considered during the risk analysis.

   The Residual Risk acceptability criteria (RPN score) was established at ≤ 19 for a low level of concern according to Bio-Rad's FMEA risk management plan. An RPN score of ≤ 19 indicates that additional mitigation activity is not required. Bio-Rad demonstrated that the RPN scores ranged from 6 for false positive results to 12 for false negative results for both the EBV VCA IgM and the Heterophile IgM Assays.

   b. *Verification and Validation Activities:*
   The QC data collected from the initial development verification and clinical validation studies for the EBV VCA IgM and Heterophile IgM Assays showed that no incidence of LSP was observed in the assay formulation.

   During the bacteria and mold challenge studies, the results from the current EBV IgM kit showed that EBV VCA IgM Assay is susceptible to extreme high levels of mold contamination.

   The modified EBV IgM Assay formulation contains protein stabilizer (goat) and protease inhibitor in the bead reagent to remediate LSP.

   Contamination studies were performed to assess the effect of bacterial and mold contaminants on reformulated EBV IgM reagent kit. The proposed EBV IgM formulation provides adequate protection against bacteria and mold contamination as compared to the reagent packs without remediation (Figures 1 to 8). Even at extreme contamination levels, remediated EBV IgM kits exhibit only minimal signal loss, but within the specifications.

Figure 1. VCA IgM, Bacteria Spiked at 1:50
Without Remediation

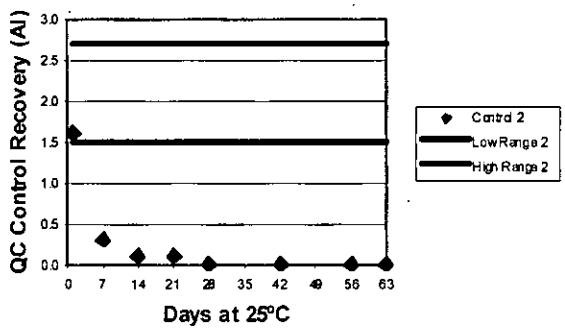


Figure 2. VCA IgM, Bacteria Spiked at 1:50
With Remediation

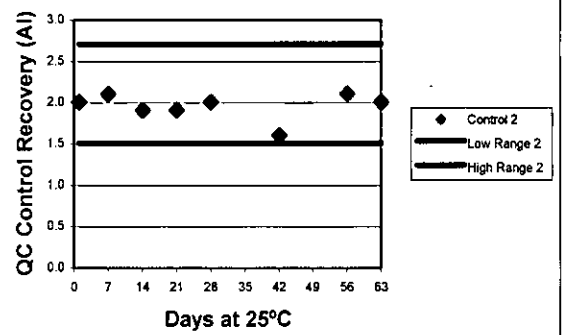


Figure 3 VCA IgM, Mold Spiked at 1:10
Without Remediation

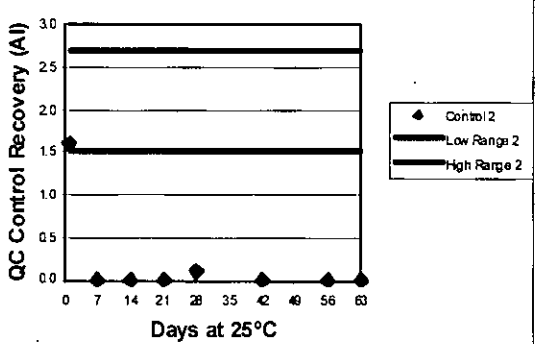


Figure 4. VCA IgM, Mold Spiked at 1:10
With Remediation

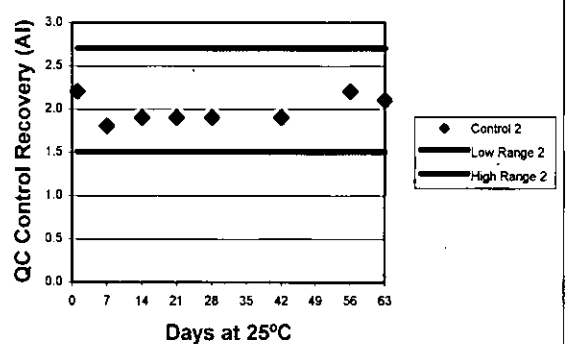


Figure 5 Heterophile IgM, Bacteria Spiked at 1:50
Without Remediation

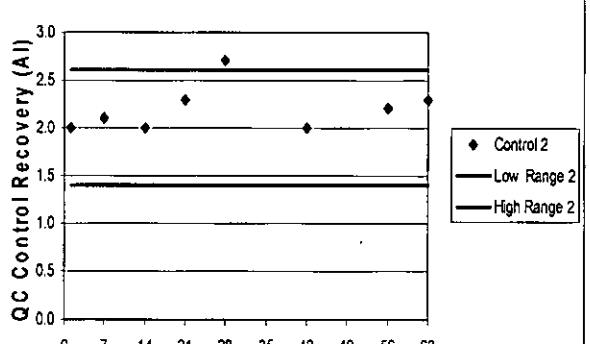
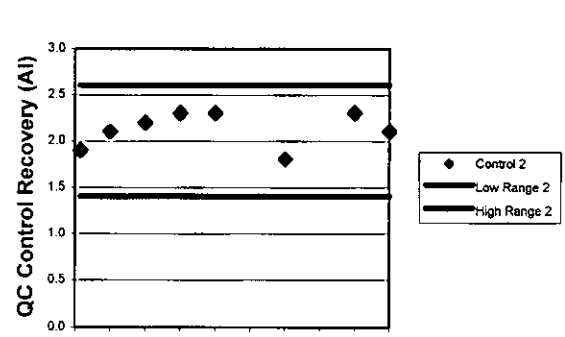
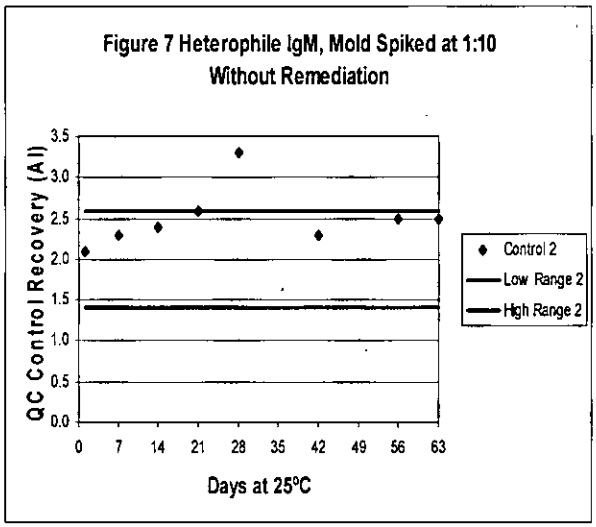
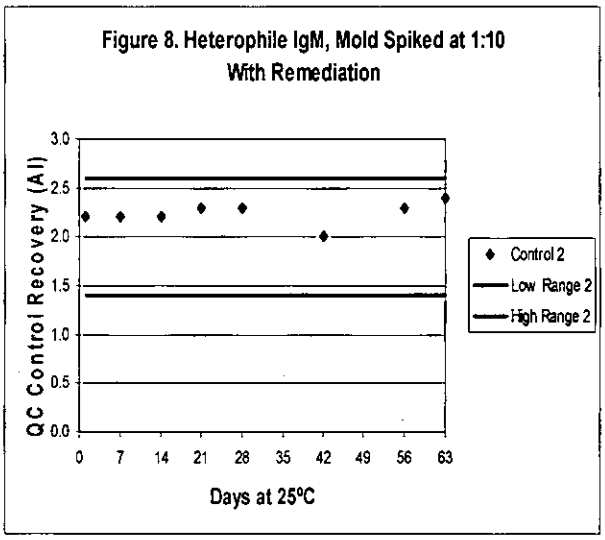


Figure 6 Heterophile IgM, Bacteria Spiked at
1:50
With Remediation







c. *Declaration of Conformity:*
A "Declaration of Conformity" certificate was submitted and signed by the Regulatory/Quality Assurance manager. The certificate states that the two manufacturing facilities are in conformance with the design control requirements as specified in 21 CFR 820.30 and "all documents and records associated with the modification of the device are available for review and inspection."

In conclusion, based on both the results of the verification/validation studies and the risk management report, Bio-Rad recommends that the required QC procedure of EBV IgM QC testing be changed from once per pack to once per day and per reagent lot once the product's formulation is updated

2. Accelerated Stability

Real time (2-8°C) and accelerated (25 °C) stability studies were carried out on predicate and modified BioPlex 2200 EBV IgM kits. The results were within the acceptable specifications and demonstrated that the addition of protein stabilizer (goat) and protease inhibitor does not have an adverse impact on product stability for the modified EBV IgM kit. The performance of the modified EBV IgM kit is equivalent to the predicate EBV IgM kit as all specifications (slope, intercept and correlation) were met. Thus, existing kit dating can be applied to the modified EBV IgM kit.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-002

NOV 2 2012

Bio-Rad Laboratories, Inc.
c/o Mr. Juang Wang
Regulatory Affairs Representative
BioPlex Division
5500 E. Second Street
Benicia, CA 94510

Re: K123021
Trade/Device Name: BioPlex® 2200 EBV IgM Kit
BioPlex® 2200 EBV IgM Calibrator Set
BioPlex® 2200 EBV IgM Control Set
Regulation Number: 21 CFR 866.3235
Regulation Name: Epstein-Barr Virus Serological Reagents
Regulatory Class: Class I
Product Code: LJN, KTN, JIX, JJY
Dated: September 26, 2012
Received: October 3, 2012

Dear Mr. Wang:

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.

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

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must

comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); 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 regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostics and Radiological Health at (301) 796-5450. 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 Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Sally A. Hojvat

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

Enclosure

INDICATIONS FOR USE STATEMENT

510(k) Number (if known): K123021

Device Name: BioPlex® 2200 EBV IgM Kit
BioPlex® 2200 EBV IgM Calibrator Set
BioPlex® 2200 EBV IgM Control Set

Indications for Use:

BioPlex® 2200 EBV IgM Kit

The BioPlex® 2200 EBV IgM kit is a multiplex flow immunoassay intended for the qualitative detection of two (2) separate analytes; Epstein-Barr Virus Viral Capsid Antigen (EBV VCA) IgM antibodies and Heterophile antibodies in human serum. The test system can be used in conjunction with the BioPlex 2200 EBV IgG kit as an aid in the laboratory diagnosis of infectious mononucleosis (IM).

The BioPlex® 2200 EBV IgM kit is intended for use with the Bio-Rad BioPlex® 2200 System.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients, cord blood, neonatal specimens, or infants. Assay performance characteristics have not been established for the diagnosis of nasopharyngeal carcinoma, Burkitt's lymphoma, and other EBV-associated lymphomas.

BioPlex® 2200 EBV IgM Calibrator Set

The BioPlex® 2200 EWBV IgM Calibrator Set is intended for the calibration of the BioPlex® 2200 EBV IgM Reagent Pack.

BioPlex® 2200 EBV IgM Control Set

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

Prescription Use _X_ AND/OR Over-the-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(Please do not write below this line-Continue on another page if needed)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic
Device Evaluation and Safety

510(k) K123021