

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

A. 510(k) Number:

k041658

B. Purpose for Submission:

New device

C. Measurands:

Anti-SS-A, anti-SS-B, anti-Sm, anti-Sm/RNP, anti-RNP, anti-ribosomal protein, anti-chromatin, anti-dsDNA, anti-centromere, anti-Scl-70, and anti-Jo1 antibodies.

D. Type of Test:

Multiplex flow, bead-based immunoassay

E. Applicant:

Bio-Rad Laboratories

F. Proprietary and Established Names:

BioPlex 2200 ANA Screen on the BioPlex 2200 Multi-Analyte Detection System

G. Regulatory Information:

1. Regulation sections:
21 CFR 866.5100 Antinuclear Antibody Immunological Test System
2. Classification:
Class II
3. Product Code:
LKJ, Antinuclear Antibody, Antigen, Control
LRM, Anti-DNA Antibody (Enzyme-Labeled), Antigen, Control
MQA, Anti-Ribosomal P Antibodies
LKO, Anti-RNP Antibody, Antigen, Control
LJM, Antinuclear Antibody (Enzyme-Labeled), Antigen, Controls
LLL, Extractable Antinuclear Antibody, Antigen and Controls
4. Panel:
Immunology 82

H. Intended Use:

1. Intended use(s):
The Bio-Rad ANA Screen is intended for the qualitative screening of specific antinuclear antibodies (ANA), the quantitative detection of antibody to dsDNA, and the semi-quantitative detection of ten (10) separate antibody

assays (Chromatin, Ribosomal Protein, SS-A, SS-B, Sm, Sm/RNP, RNP, Scl-70, Jo-1, and Centromere B,) in human serum and/or EDTA or heparinized plasma. The test system is used as an aid in the diagnosis of systemic rheumatic diseases. The ANA Screen is intended for use with the Bio-Rad BioPlex 2200 System.

2. Indication(s) for use:

The Bio-Rad ANA Screen is intended for the qualitative screening of specific antinuclear antibodies (ANA), the quantitative detection of antibody to dsDNA, and the semi-quantitative detection of ten (10) separate antibody assays (Chromatin, Ribosomal Protein, SS-A, SS-B, Sm, Sm/RNP, RNP, Scl-70, Jo-1, and Centromere B,) in human serum and/or EDTA or heparinized plasma. The ANA Screen is intended for use with the Bio-Rad BioPlex 2200 System.

Uses:

The test system is used to screen serum or plasma (EDTA and heparin) samples and detect the presence of antinuclear antibodies as an aid in the diagnosis of systemic rheumatic diseases (systemic lupus erythematosus (SLE), Sjogren's syndrome, mixed connective tissue disease (MCTD), undifferentiated connective tissue disease, scleroderma, dermatomyositis, polymyositis, rheumatoid arthritis, CREST syndrome, and Raynaud's phenomenon) in conjunction with clinical findings and other laboratory tests.

3. Special condition for use statement(s):

For prescription use only

4. Special instrument Requirements:

BioPlex 2200 Multi-Analyte Detection System

I. Device Description:

The device components include the following: Bead Set containing dyed beads coated with dsDNA, Chromatin, Ribosomal Protein, SS-A 60, SS-A 52, SS-B, Sm, SmRNP, RNP A, RNP 68, Scl-70, Jo-1, Centromere B, Internal Standard (ISB), Serum Verification (SVB), and a Reagent Blank Bead (RBB), with glycerol and protein stabilizers; Conjugate containing murine monoclonal anti-human IgG/phycoerythrin (PE) conjugate and sheep anti-human FXIII/phycoerythrin conjugate in a phosphate buffer; Sample Diluent; Calibrator Set of 6 vials containing antibodies to dsDNA, and a set of 4 vials for the other 12 analytes; Positive and Negative Controls; Sheath Fluid; Wash Solution; and the BioPlex 2200 system.

J. Substantial Equivalence Information:

1. Predicate device name(s) and K numbers:

Instrument

BioPlex2200 System	Comparative FDA Cleared PREDICATE DEVICE	510(k) Number
BioPlex 2200 ANA Screen on the BioPlex 2200 System	Zeus Athena Multi-Lyte ANA Test System	K011244
	Diagnostic Products Corporation (DPC) Immulite 2000 Automated Immunoassay Analyzer	K970227

Assay

BioPlex2200 ANA Screen	Comparative FDA Cleared Device	510(k) Number
ANA Screen (based on results of all analytes listed below)	Bio-Rad (Helix) Autoimmune EIA ANA Screening Test	954723

Analytes

BioPlex2200 ANA Screen Analyte	Comparative FDA Cleared PREDICATE DEVICE	510(k) Number
SSA (SSA 60 and SSA 52)	Inova Diagnostics, Inc. QUANTA Lite™ SSA	922830
SSB	Bio-Rad (Helix) Autoimmune EIA SS-B / La Test	932419
Sm	Inova Diagnostics, Inc. QUANTA Lite™ Sm	922831
SmRNP	Inova Diagnostics, Inc. QUANTA Lite™ RNP (Sm/RNP)	922833
RNP (RNP 68 and RNP A)	Pharmacia Varelisa® RNP Antibodies	993589
Ribosomal Protein	Inova Diagnostics, Inc. QUANTA Lite™ Ribosome P	981237
Chromatin	Inova Diagnostics, Inc. QUANTA Lite™ Chromatin ELISA	982603
dsDNA (quantative /semi-quantitative)	Pharmacia Varelisa® ds-DNA ANTIBODY EIA Kit	950031
Centromere	Bio-Rad (Helix) Autoimmune EIA Anti-Centromere Test	000489
Scl-70	Bio-Rad (Helix) Autoimmune EIA Anti-Scl-70 Test	951798
Jo-1	Bio-Rad (Helix) Autoimmune EIA Anti-Jo-1 Test	951850

2. Predicate K number(s):
See table above
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Instruments	<u>BioPlex 2200 System</u>	
Detection	Based on Luminex Corporation's multiplex, bead-based technology	<u>Zeus AtheNA Multi-Lyte:</u> Based on Luminex Corporation's multiplex, bead-based technology
Sample handling/	Automated sample	<u>Immulin 2000 Automated</u>

Similarities		
Item	Device	Predicate
processing	handling and processing	<i>Immunoassay Analyzer</i> Automated sample handling and processing
Reagent storage	On-board, refrigerated reagent storage	<i>Immolute 2000 Automated Immunoassay Analyzer</i> On-board, refrigerated reagent storage
Components/materials		<i>Autoimmune EIA's:</i>
Reagents	Wash buffer, sample diluent	Wash buffer, sample diluent
Calibrators	Quantitative and semi-quantitative analytes	Quantitative and semi-quantitative analytes
Controls	Single negative control	Single negative control
Function and Use		<i>Autoimmune EIA's:</i>
Intended use	Quantitative (dsDNA only) and semi-quantitative autoimmune antibody detection	Quantitative (dsDNA only) and semi-quantitative autoimmune antibody detection
Matrix	Serum and plasma (EDTA and heparin) for all analytes	Serum and plasma (Jo-1, dsDNA, RNP, SS-B)
Differences		
Item	Device	Predicate
Instruments	<i>BioPlex 2200 System</i>	
Detection	Based on Luminex Corporation's multiplex, bead-based technology	<i>Immolute 2000 Automated Immunoassay Analyzer:</i> luminometer (photomultiplier tube) to detect chemiluminescence
Sample handling/processing	Automated sample handling and processing	<i>Zeus AtheNA Multi-Lyte:</i> No automated sample handling or processing capabilities
Reagent storage	On-board, refrigerated reagent storage	<i>Zeus AtheNA Multi-Lyte:</i> Off-line reagent storage
Components/materials		<i>Autoimmune EIA's:</i>
Solid phase	Dyed antigen coated beads	96 well antigen coated microwells
Conjugate	Anti-human IgG/phycoerythrin	Anti-human IgG/horseradish peroxidase with TMB substrate
Calibrators	Qualitative and semi-quantitative analytes	Cut-off /low positive controls (qualitative analytes)
Controls	One multi-analyte positive control containing all 11 analytes	One positive control per analyte
Sheath fluid	Used to suspend the bead reagent and introduce it	Not utilized in EIA's

Similarities		
Item	Device	Predicate
	into the detector	
Function and use		<u>Autoimmune EIA's</u>
Matrix	Serum and plasma (EDTA and heparin) for all analytes	Serum (ANA Screen, SS-A, Sm, Sm/RNP, Ribosome P, Chromatin, Centromere, Scl-70)

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

NCCLS EP5-A and NCCLS EP7-A.

L. Test Principle:

The ANA Screen detects the presence of circulating autoantibodies in serum or plasma using a group of autoantigens. Beads are individually coated with individual antigens, so that the presence of each antinuclear and autoimmune antibody can be individually determined. Fluorescence detection facilitates the differentiation of normal and abnormal antibody concentrations.

The ANA Screen uses multiplex flow immunoassay, a methodology that resembles traditional EIA, but permits simultaneous detection and identification of several antibodies in a single tube. Thirteen (13) different populations of dyed beads are coated with antigens associated with systemic autoimmune disease (dsDNA, Chromatin, Ribosomal Protein, SS-A 60, SS-A 52, SS-B, Sm, Sm/RNP, RNP A, RNP 68, Scl-70, Jo-1 and Centromere B)*. The BioPlex 2200 System combines an aliquot of patient sample, sample diluent, and bead reagent into a reaction vessel and the mixture is incubated at 37°C. After a wash cycle, murine monoclonal 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 re-suspended in wash buffer.

The bead mixture is suspended in sheath fluid, passes through the detector and the identity of the dyed beads is determined by the fluorescence of the dyes. Based on its fluorescent signature, each bead is classified to its own unique region. The detector measures at least 200 beads for each analyte, per specimen. The BioPlex 2200 ANA Screen utilizes one of these regions for each of the 13 analytes it detects. Three additional regions are assigned to beads used for quality control purposes. While the identity of the dyed beads is determined by the unique fluorescence intensity of the dyes, 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) and fluorescence ratio (FR).

Three additional dyed beads, Internal Standard Bead (ISB), Serum Verification Bead (SVB) and a Reagent Blank Bead (RBB) are present in each reaction mixture to verify detector response, the addition of serum or plasma to the reaction vessel and the absence of significant non-specific binding in serum or plasma. The instrument is calibrated using sets of distinct calibrators. For dsDNA, six (6) vials, representing six (6) different levels of antibody concentrations, are used for quantitative calibration, and results for patient samples are expressed in IU/mL. Results of ≤ 4 IU/mL are

negative, 5 - 9 IU/mL are indeterminate, and results of 10 IU/mL or higher are considered positive for dsDNA antibody. For the other twelve (12) beads, four (4) vials representing four (4) different antibody concentrations are used for semi-quantitative calibration. The result for each of these antibodies is expressed as an antibody index (AI). An AI of 1.0 indicates an antibody cut-off concentration that corresponds to approximately the 99th percentile of values obtained from a non-diseased population; results of 1.0 or higher are reported as positive. Results of <1.0 are reported as negative.

* In cases where either SS-A 60 and/or SS-A 52 are positive, results are reported as positive for SS-A; and when either RNP A and/or RNP 68 are positive, results are reported as positive for RNP.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility

Reproducibility testing for the BioPlex 2200 ANA Screen was conducted at three clinical sites located in the U.S. A reproducibility panel consisting of 33 panel members was prepared at Bio-Rad Laboratories. Each of 10 positive panel members was prepared by combining one or more antibody positive patient samples for one or more of the 13 analytes contained in the BioPlex 2200 ANA Screen (dsDNA, Chromatin, SS-A 52, SS-A 60, SS-B, Sm, RNP 68, RNP A, Sm/RNP, Centromere, Ribosomal Protein, Scl-70, Jo-1 antibodies). Five of the 10 members had levels near the cut-off. One panel member was negative for all 13 analytes. Each panel was made in serum (N=11), EDTA (N=11) and lithium heparin (N=11); a total of 33 panel members. In addition, three controls (positive, dilute positive, and negative) were included and tested as panel members (a total of 36 panel members).

Each testing facility evaluated reproducibility using a different kit lot of the Bio-Rad ANA Screen. The 36 panel members (including the Autoimmune Control Set) were tested in duplicate on 2 runs per day (one in the morning and one in the afternoon), for 10 days using one lot of BioPlex 2200 ANA Screen Reagent Pack and one lot of BioPlex 2200 ANA Screen Calibrator set at each of the 3 sites (2 times x 2 runs x 10 days = 40 replicates per panel member per site). The combined total of replicates for all three sites is 120 replicates per panel member. The data were analyzed for intra-assay and inter-assay reproducibility according to NCCLS EP5-A Vol. 19 No. 2, p 24 Eq. C2 and p.25 Eq's. C3 and C4. Intra-run %CV ranged from 1.2 to 11.1% and inter-run %CV ranged from 2.8 to 12.8%

Site	A	B	C
Instrument	1	2	3
Reagent Pack Lot	X	Y	Z
Serum			
Intra-run %CV	1.7 – 7.9%	2.1 – 8.6%	2.1 – 11.1%
Inter-run %CV	2.8 - 12.8%	5.8 - 11.9%	3.6 - 12.0%
EDTA Plasma			
Intra-run %CV	1.7 - 9.4%	2.7 - 7.3%	1.2 - 7.6%
Inter-run %CV	3.7 - 10.9%	5.5 - 11.6%	3.8 - 9.6%
Lithium Heparin Plasma			
Intra-run %CV	2.0 - 7.5%	2.3 - 9.0%	2.1 - 7.2%
Inter-run %CV	3.2 - 8.9%	6.2 - 12.2%	3.9 - 8.3%

b. Linearity/assay reportable range:

All analytes except dsDNA antibodies are reported as positive or negative compared to an internally established cut-off value with a measuring range of 0.2 – 8.0 AI (antibody index). Linearity for the anti-dsDNA assay was demonstrated.

In order to find samples within the measuring range of the assay (1 IU/mL to 300 IU/mL), 4 very high dsDNA positive patient samples were initially diluted with negative serum. The samples were then diluted to the following dilution ratios: neat, 1:1.25, 1:1.67, 1:2.5, 1:5, and 1:10. Each dilution was tested a minimum of 4 times. The replicates were separated by time and the dilutions were randomized on the sample racks. Percent recoveries ranged from 83 to 105%.

Sample n=6	% Recovery range
1	83 – 100%
2	93 – 100%
3	90 – 100%
4	97 – 105%

In addition, serial dilutions of the WHO W0/80 dsDNA Standard were made to obtain dsDNA antibody concentrations throughout the assay range. The dilutions were assayed and the actual results compared to the expected results. Linear regression analysis of the comparison yielded $y = 0.9854x + 2.773$, $r^2 = 0.9994$.

c. Traceability (controls, calibrators, or method):

Traceability for dsDNA values in the calibrator set were established using the WHO First International Standard for Anti-double stranded DNA (dsDNA), Human Code: W0/80 (W1065). The WHO W0/80 standard is a lyophilized powder and is reconstituted to a concentration of 200 IU/mL. Serial dilutions of this material were

NT= Not Tested

Testing for interfering substances was conducted according to NCCLS EP7-A (Vol. 22, no. 27). No significant interference was observed in any of the substances tested. The following substances were tested (N=20) at up to and including the maximum levels in duplicate on one lot.

Substance	Concentration
Hemoglobin	≤ 500 mg/dl
Bilirubin (unconjugated)	≤ 20 mg/dl
Triglycerides	≤ 3000 mg/dl
Protein (total)	≤ 12 g/dl
Cholesterol	≤ 500 mg/dl
Red blood cells	≤ 0.4% concentrate
Gamma-globulin	≤ 2.5 g/dl
Ascorbic acid	≤ 3.0 mg/dl

f. Assay cut-off:

A total of 719 samples were used for the study. The negative population consisted of 285 samples from normal donors and confirmed to be negative by the predicate screening device. The remaining 434 samples were positive for one or more of the analytes by predicate EIA methods.

Antigen	Total number of EIA positive samples
dsDNA	100
Chromatin	50
RNP A + RNP 68	115
SSB	110
SSA 52 + SSA 60	49
Scl-70	95
Sm	52
Centromere	93
Sm/RNP	51
Ribosome Protein	83
Jo-1	99

The 719 samples were assayed in singlicate. Calibrators, controls and WHO dsDNA standards were assayed in quadruplicate, duplicate and duplicate, respectively, in each run. There were a total of 11 runs on 3 different instruments over a period of 16 days.

Cut-offs were established as follows: for dsDNA, results of ≤ 4 IU/mL are negative, 5-9 IU/mL are indeterminate, and results of ≥ 10 IU/mL are reported as positive; and for all other assays, results of < 1.0 AI (antibody index) are negative, and results of 1.0 or greater are reported as positive. Using these cut-offs, Receiver Operator Curve (ROC) analysis of the data showed sensitivities ranging from 67% to 100%. Specificities ranged from 94% to 100%.

Antigen	Sensitivity	Specificity
dsDNA	67%	99%
Chromatin	94%	100%
RNP A + RNP 68	96%	94%
SSB	100%	98%
SSA 52 + SSA 60	99%	98%
Scl-70	98%	98%
Sm	96%	100%
Centromere	98%	98%
Sm/RNP	96%	99%
Ribosome Protein	82%	98%
Jo-1	95%	100%

2. Comparison studies:

a. *Method comparison with predicate devices:*

Comparison of ANA Screen and ANA Microplate EIA Screen:

The ability of BioPlex 2200 System ANA Screen qualitative screening format to detect positive results in serum samples collected prospectively from patients was compared to results of testing with the Bio-Rad (Helix) Autoimmune EIA ANA Screening test. A total of 908 prospective serum samples were tested at 3 U.S. clinical testing sites. The samples were collected from patients seen at a rheumatology clinic and suspected of having systemic autoimmune disease. Results are summarized in the table below.

	Positive ANA Screen	Negative ANA Screen	Total
Positive EIA	351	149	500
Negative EIA	39	369	408
Total	390	518	908

Positive Agreement: $351/500 = 70.2\%$ (95% CI: 66.1 – 74.4%)
 Negative Agreement: $369/408 = 90.4\%$ (95% CI: 87.5 – 93.4%)
 Over-all Agreement: $720/908 = 79.3\%$ (95% CI: 76.6 – 82%)

Results presented below are for patients with a diagnosis of targeted connective tissue disease (SLE, scleroderma, Raynaud's phenomenon, CREST, Sjogren's syndrome, mixed connective tissue

disease, undifferentiated connective tissue disease and/or dermatomyositis/polymyositis) as well as for those patients diagnosed with connective tissue disease other than the targeted diseases and for those patients in whom connective tissue disease was not a diagnosis. Results for targeted connective tissue disease are presented for both those diagnosed by a qualified M.D. rheumatologist (**Physician Diagnosed Targeted CTD**) and those diagnosed using adherence to American College of Rheumatology or literature disease classification criteria (**Criteria Diagnosed Targeted CTD**). A diagnosis of connective tissue disease other than the targeted diseases was made on the basis of physician diagnosis.

Comparison of BioPlex 2200 ANA Screen (Qualitative Screening Format) to Bio-Rad (Helix) Autoimmune EIA ANA Screening Test in Patients with Physician Diagnosed Targeted CTD (n=413):

	BioPlex 2200 ANA Screen		
Bio-Rad (Helix) EIA	Positive	Negative	Total
Positive	256	76	332
Negative	9	72	81
Total	265	148	413

Positive Agreement: 77.1% (256/332)
 Negative Agreement: 88.9% (72/81)
 Overall Agreement 79.4% (328/413)

Comparison of BioPlex 2200 ANA Screen (Qualitative Screening Format) to Bio-Rad (Helix) Autoimmune EIA ANA Screening Test in Patients with Criteria Diagnosed Targeted CTD (n=408):

	BioPlex 2200 ANA Screen		
Bio-Rad (Helix) EIA	Positive	Negative	Total
Positive	268	67	335
Negative	9	64	73
Total	277	131	408

Positive Agreement: 80.0% (268/335)
 Negative Agreement: 87.7% (64/73)
 Overall Agreement 81.4% (332/408)

Comparison of Selected Antibodies to EIA Methods (n=1047):

Testing to evaluate the performance of the BioPlex 2200 ANA Screen compared to the individual predicate EIAs was conducted at three sites located in the U.S. using 907 samples collected prospectively from consecutive patients being seen in a rheumatology clinic and suspected of, or with a history consistent

with an autoimmune/connective tissue disease. Additional selected retrospective (frozen) samples, known to be positive for one or more of the 11 analytes detected by the Bio-Rad BioPlex 2200 ANA Screen were selected for inclusion in the study. Forty positive samples for each of the 11 analytes were included (440 total positive samples) in the study. One-hundred selected retrospective samples, known to be ANA EIA negative, were also included in the study. This resulted in n=1047 (907+40+100) for each analyte.

Combined Prospective and Retrospective Comparison Testing

Antibody/ antibody group	ds- DNA	Chrom	Rib- P	SSA	SSB	Sm	Sm/ RNP	RNP	Scl- 70	Jo-1	Cent.
N =	955	1046	1046	1047	1048	1047	1047	1017	1047	1038	1048
Bio-Rad and EIA positive	102	109	32	193	96	60	128	116	22	36	67
Bio-Rad positive and EIA negative	25	72	22	17	20	25	13	27	18	0	10
Bio-Rad and EIA negative	800	788	986	821	920	947	881	854	995	997	970
Bio-Rad negative and EIA positive	28	77	6	16	12	15	25	20	12	5	1
%Positive agreement	78.5	58.6	84.2	92.3	88.9	80	83.7	85.3	64.7	87.8	98.5
%Negative agreement	96.7	91.6	97.8	97.8	97.9	97.4	98.5	96.9	98.2	100	99
% Overall agreement	94.5	85.7	97.8	96.8	96.9	96.2	96.4	95.4	97.1	99.5	98.9
95% CI	93-96	84-88	96-98	96-98	96-98	95-97	95-98	94-97	96-98	99- 99.9	98- 99.6
Ind./equiv. -results omitted	92*							31**			
Low SVB*** - results omitted	1	2	2	1		1	1		1	10	

*92 BioPlex dsDNA or predicate dsDNA results omitted from the calculations

**31 predicate RNP results omitted from the calculations

*** 19 low Serum Verification Bead results omitted from the calculations

Additional anti-dsDNA assay comparisons:

A correlation was made of the BioPlex ANA dsDNA assay versus the Pharmacia Varelisa dsDNA EIA by testing the prospective population of 907 samples. For test results under 25 IU/mL, and

where indeterminate and equivocal results were included (n=850), the linear regression analysis showed $y = 0.05x + 1.08$, $r = 0.536$. For all results and where indeterminate and equivocal results were excluded (n=812), the linear regression analysis showed $y = 0.23x - 0.76$ and $r = 0.544$. In another study, the BioPlex ANA Calibrators were run on the Pharmacia Varelisa dsDNA assay and recoveries ranged from 36% to 92%. The BioPlex calibrators were also run on a second commercially available dsDNA antibody assay and recoveries ranged from 27% to 121%.

Bio-Rad states that the differences between the dsDNA antibody assays can be caused by several factors including the type of capture antigen, whether the assays detect both ssDNA and dsDNA antibodies simultaneously and how well the assays capture high versus low avidity dsDNA antibodies. This description and information is included in the package insert.

b. Matrix comparison:

A subset of 214 subjects from the prospective population was collected and tested as matched serum, EDTA (N=214), and sodium heparinized plasma (N=214) samples. Compared to the serum values recoveries for the EDTA specimens ranged from 95.3% to 100.2% and for sodium heparin, recoveries ranged from 90.5% to 103.6%. The performance of the assay using lithium heparin plasma was demonstrated in the reproducibility studies.

Analyte	EDTA % Recovery	Sodium Heparin % Recovery
dsDNA	98.0%	96.1%
Chromatin	100.2%	90.5%
Ribosomal-P	98.3%	101.2%
SSA	98.3%	100.2%
SSA-52	97.1%	102.0%
SSA-60	99.0%	100.5%
SSB	98.3%	102.6%
Sm	100.2%	101.4%
Sm/RNP	99.8%	103.6%
RNP	99.1%	100.2%
RNP-A	99.1%	100.4%
RNP-68	98.5%	100.3%
Scl-70	95.3%	95.9%
Jo-1	99.2%	100.0%
Centromere B	97.4%	98.0%

3. Clinical studies:

a. Clinical sensitivity and specificity:

The clinical sensitivity and specificity was calculated by running 908 prospectively collected disease positive samples and comparing the result to the clinical status. These calculations do not take into consideration the prevalence (incidence) antibodies found in the disease states.

BioPlex 2200 versus Patient Clinical Status

Disease status:	BioPlex Positive	BioPlex Negative	Total
Positive	277	131	408
Negative	113	387	500
Total	390	518	908

Sensitivity: 67.9% (277/408) [95% CI 63.2 – 72.6%]

Specificity: 77.4% (387/500) [95% CI 73.6 – 81.2%]

b. Other clinical supportive data (when a is not applicable):
Not applicable.

4. Clinical cut-off:
See assay cut-off

5. Expected values/Reference range:
Expected values for the ANA Screen test are presented in the following table for a U.S. population of normal blood donors (N=222). For dsDNA, results of ≤ 4 IU/mL are negative, 5 – 9 IU/mL are indeterminate, and ≥ 10 IU/mL or higher are reported as positive. For the other assays, results of < 1.0 are negative and results of ≥ 1.0 AI are reported as positive.

Result	Positive		Negative		Indeterminate	
N = 222	#	(%)	#	(%)	#	(%)
ANA Screen*	15	6.8	207	93.2	N/A	N/A
dsDNA	3	1.4	211	95.0	8	3.6
Chromatin	2	0.9	220	99.1	N/A	N/A
Ribosomal protein	0	0	222	100.0		
SS-A	2	0.9	220	99.1		
SS-B	0	0	222	100		
Sm	1	0.5	221	99.5		
SmRNP	2	0.9	220	99.1		
RNP	6	2.7	216	97.3		
Scl-70	1	0.5	221	99.5		
Jo-1	0	0.0	222	100.0		
Centromere B	3	1.4	219	98.6		

*results calculated based on testing of all analytes.

Expected values for the ANA Screen test are presented in the following table for patients from the BioPlex 2200 ANA Screen prospective study conducted at three clinical sites (N=908).

Result	Positive		Negative		Indeterminate	
N = 908	#	(%)	#	(%)	#	(%)
ANA Screen	390	43.0	518	57.0%	N/A	N/A
dsDNA	119	13.1	741	81.6%	49	5.4%
Chromatin	168	18.5	740	81.5%	N/A	N/A
Ribosomal Protein	37	4.1%	871	95.9%		
SS-A	173	19.0	735	81.0%		
SS-B	76	8.4%	832	91.6%		
Sm	60	6.6%	848	93.4%		
SmRNP	103	11.3	805	88.7%		
RNP	112	12.3	796	87.7%		
Scl-70	23	2.5%	885	97.5%		
Jo-1	6	0.7%	902	99.3%		
Centromere B	38	4.2%	870	95.8%		

N. Instrument Name:

BioPlex™ 2200 Multi-Analyte Detection System

O. System Descriptions:

1. Modes of Operation:

Calibrators, controls and patient samples are loaded by the operator into the sample racks and then loaded onto the instrument. The operator schedules calibration (if needed), quality control (QC) and patient samples by interaction with instrument software. Samples are processed automatically by the instrument. Results are displayed for the QC and patient samples in tabular format with warnings and/or error messages appearing if problems occur. Results are verified by the operator and can be printed out or sent to a laboratory information system if present.

2. Software:

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

3. Sample Identification:

Samples are identified by a bar code reader from a bar code label on each sample tube.

4. Specimen Sampling and Handling:

Specimen sampling and processing is automatically performed by the instrument.

5. Assay Types:
The BioPlex 2200 uses a multiplex bead-based flow immunoassay.
6. Reaction Types:
Antigen/antibody binding is detected and measured.
7. Calibration:
Calibration is performed by loading calibrator sets and assaying at a minimum in duplicate every 14 days or with each new reagent pack lot. For dsDNA antibodies, a 6-point 4PL fitted curve is used to calculate quantitative results. For the other analytes, a point-to-point curve fit using four calibrators is used to calculate semi-quantitative results.
8. Quality Control:
The control set should be run at the beginning of each day that the BioPlex 2200 assays are used. The ANA Screen Control Set should be run at least once per day, and with each new reagent pack lot.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The “L. Performance Characteristics” Section Of The SE Determination Decision Summary:

Q. Conclusion:

The submitted material in this premarket notification is complete and supports a substantial equivalence decision. The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10. Each human donor unit used to manufacture the BioPlex reagents was tested by FDA accepted methods and found non-reactive for Hepatitis B surface antigen (HBsAg), antibody to Hepatitis C (HCV) and antibody to HIV-1/HIV-2.