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BIOPLEX™ 2200 MEDICAL DECISION SUPPORT SOFTWARE FOR USE WITH THE BIOPLEX 2200 MULTI-ANALYTE DETECTION SYSTEM 510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

510(k) Number	510(k) Summary Report Date
k043341	October 24, 2005

1.0 MANUFACTURER INFORMATION

Medical Decision Support Software (MDSS) Manufacturing Site	
Manufacturer Address	Bio-Rad Laboratories, Inc. Clinical Systems Division 4000 Alfred Nobel Drive Hercules, CA 94547
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Establishment Registration No.	2915274
Owner / Operator	Bio-Rad Laboratories, Inc. 4000 Alfred Nobel Drive Hercules, CA 94547
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Official Correspondent Address	Bio-Rad Laboratories 6565 185th Ave NE Redmond, WA 98052
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Owner / Operator	Bio-Rad Laboratories, Inc. 4000 Alfred Nobel Drive Hercules, CA 94547
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2.0 CLASSIFICATION INFORMATION

BioPlex 2200 Medical Decision Support Software (MDSS) Classification

Classification Name	Amphetamine Test System
Common Name:	Medical Decision Support Software
Product Trade Name	BioPlex 2200 Medical Decision Support Software (MDSS) on the BioPlex 2200 Multi-Analyte Detection System
Device Class	Class II
Classification Panel	Clinical Toxicology
Regulation Number	862.3100

BioPlex 2200 ANA Screen Classification

Classification Name	Antinuclear Antibody (Enzyme-Labeled), Antigen, Controls
Common Name:	Multi-Analyte Detection System, ANA Screen
Product Trade Name	BioPlex 2200 ANA Screen on the BioPlex 2200 Multi-Analyte Detection System
Device Class	Class II
Classification Panel	Immunology and Microbiology
Regulation Number	866.5100

3.0 LEGALLY MARKETED EQUIVALENT (SE) DEVICES

BioPlex 2200 System	Comparative FDA Cleared Device	510(k) Number	Product Code	Decision Date
Medical Decision Support Software (MDSS)	Remedi HS™ Drug Profiling System	K941596	DNI	March 27, 1995

4.0 DEVICE DESCRIPTION

Note: The following product description is limited to the BioPlex 2200 ANA Screen Medical Decision Support Software (MDSS). A description of the BioPlex 2200 ANA Screen on the BioPlex 2200 Multi-Analyte Detection System is included in the pre-market notification submission K041658. Please refer to K041658 for a description of the BioPlex 2200 ANA Screen.

The BioPlex 2200 Medical Decision Support Software (MDSS) is a pattern recognition algorithm that can enhance the performance of the ANA Screen by identifying associated diagnostic patterns among its multiple assay results. The MDSS can suggest one or more possible disease associations after identifying patterns from the eleven (11) individual antibody results. The MDSS is based on the principles of the "k-nearest neighbor"[11] (kNN) statistical technique. Each "unknown" is compared to a pre-established database that contains the results for over 1,400 characterized sera/plasma. Results of MDSS analysis fall into one of the following general outcomes: Negative, No Association, or Association with Disease. When the results of the MDSS analysis fall into the Association with Disease category, the MDSS software will propose a maximum of two disease classifications based upon the similarity of the current analysis to the stored results. The MDSS output can also aid in determining appropriate additional autoimmune serological testing. All possible MDSS disease associations with corresponding definitions are listed in the following table. Note: MDSS outputs 9 through 15 were not observed in the clinical trial.

Table: MDSS Output

#	MDSS Text Output	Internal Output Abbreviations
1	All antibody levels for systemic autoimmune disease are below pre-established cutoffs. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	Negative
2	Antibody levels show no association with MDSS profiles for systemic autoimmune diseases. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	No Association (NA)

#	MDSS Text Output	Internal Output Abbreviations
3	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider SLE. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	SLE
4	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider SLE or Sjogren's syndrome. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	SS / SLE
5	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider Polymyositis. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	Polymyositis
6	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider Scleroderma. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	Scleroderma
7	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider MCTD or SLE. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	MCTD / SLE
8	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider SLE or Scleroderma. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	SLE / Scleroderma
9*	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider Polymyositis or SLE. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	Polymyositis / SLE
10*	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider Polymyositis or MCTD. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	Polymyositis / MCTD
11*	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider Polymyositis or Sjogren's syndrome. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	Polymyositis / SS

#	MDSS Text Output	Internal Output Abbreviations
12*	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider Polymyositis or Scleroderma. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	Polymyositis / Scleroderma
13*	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider MCTD or Sjogren's syndrome. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	MCTD / SS
14*	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider MCTD or Scleroderma. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	MCTD / Scleroderma
15*	Antibody levels show association with MDSS profiles for systemic autoimmune disease. Consider Scleroderma or Sjogren's syndrome. MDSS outputs of "Negative" or "No Association" do not rule out autoimmune disease. Patients with Rheumatoid Arthritis may result in an SLE association from MDSS, thus MDSS associations from patients with RA should be interpreted with caution.	Scleroderma / SS

**Note: these MDSS outputs were not observed in the clinical trial.*

5.0 INTENDED USE

The BioPlex™ 2200 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, SmRNP, 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 autoimmune diseases.

The ANA Screen is intended for use with the Bio-Rad BioPlex 2200 System.

The BioPlex 2200 Medical Decision Support Software (MDSS), used in conjunction with the ANA Screen, is an optional laboratory tool that associates patient antibody results with predefined MDSS profiles that have been correlated with the following systemic autoimmune diseases: Systemic Lupus Erythematosus (SLE), Mixed Connective Tissue Disease (MCTD), Sjögren's Syndrome (SS), Scleroderma (Systemic Sclerosis) and Polymyositis.

5.1 Indications For Use

The BioPlex™ 2200 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, SmRNP, RNP, Scl-70, Jo-1, and Centromere B) in human serum and/or EDTA or heparinized plasma.

The ANA Screen is used to screen serum or plasma (EDTA, heparin) samples and detect the presence of antinuclear antibodies as an aid in the diagnosis of systemic autoimmune diseases (Systemic Lupus Erythematosus [SLE], Mixed Connective Tissue Disease [MCTD], Undifferentiated Connective Tissue Disease [UCTD], Sjögren's Syndrome [SS], Scleroderma [Systemic Sclerosis], Dermatomyositis, Polymyositis, Rheumatoid Arthritis [RA], CREST Syndrome, and Raynaud's Phenomenon) in conjunction with clinical findings and other laboratory tests.

The ANA Screen is intended for use with the Bio-Rad BioPlex 2200 System.

The BioPlex 2200 Medical Decision Support Software (MDSS), used in conjunction with the ANA Screen, is an optional laboratory tool that associates patient antibody results from the ANA Screen with predefined MDSS profiles that have been correlated with the following systemic autoimmune diseases: Systemic Lupus Erythematosus (SLE), Mixed Connective Tissue Disease (MCTD), Sjögren's Syndrome (SS), Scleroderma (Systemic Sclerosis) and Polymyositis.

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6.0 TECHNOLOGICAL CHARACTERISTICS

Note: The following comparison information is limited to the BioPlex 2200 ANA Screen Medical Decision Support Software (MDSS). Comparison information for the BioPlex 2200 ANA Screen on the BioPlex 2200 Multi-Analyte Detection System is included in the pre-market notification submission K041658. currently under review by the U.S. Food and Drug Administration.

The following table summarizes similarities and difference between the Bioplex 2200 Medical Decision Support Software and the Remedi HS™ Drug Profiling System (K 941596).

Table 1(a): Similarities between data processing modules

Similarities between Data Processing Modules	**BioPlex 2200 Medical Decision Support Software**	**Remedi HS Drug Profiling System**
Input	Library or training set data on test results from 1,130 patients.	Library of known drug spectra stored in memory.
Function	Data processing module for association of patient specific information with the current condition of the patient.	Data processing module for association of patient specific information with the current condition of the patient.
Technology	Computer based, software driven, data driven algorithm.	Sophisticated computer algorithm.
Output	Test results as compared to training set.	Test results as compared to known library.

Table 1(b): Differences between data processing modules

Differences between Data Processing Modules	**BioPlex 2200 Medical Decision Support Software**	**Remedi HS Drug Profiling System**
Input	Results from serological analysis of patient serum or plasma for specific autoantibodies.	Results from chromatographic analysis of patient urine or serum for drugs.
Function	Identification of possible disease associations.	Identification of possible drugs in the biological specimen.
Algorithm Technology	k-Nearest Neighbor data analysis algorithm and pre-established medical database.	Peak Identification for comparison of unknown to spectral library of drugs.
Output	List of test results in IU/ml and AI (antibody index).	List of test results in the form of a Chromatogram.

7.0 PERFORMANCE SUMMARY

Note: Performance testing summarized in this section is limited to additional clinical concordance and MDSS related claims added to the package insert since submission of K041658, BioPlex 2200 ANA Screen on the BioPlex 2200 Multi-Analyte Detection System. Please refer to K041658 for performance testing information relating to the original BioPlex 2200 ANA Screen submission.

Clinical testing to evaluate the clinical performance of the BioPlex 2200 Medical Decision Support Software (MDSS) for use with the BioPlex 2200 Multi-Analyte Detection System, as well as the concordance of the BioPlex 2200 ANA Screen with clinical diagnosis for seven targeted diseases was conducted at three sites located in the U.S. The study was conducted using 908 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. A subset of 214 subjects from this prospective population was collected and tested as matched serum, EDTA (N=214), and sodium heparinized plasma (N=214) samples.

Additionally, 222 normal blood donors were added to the MDSS analysis where they were presumed to be negative for autoimmune disease.

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7.1 BioPlex 2200 Ana Screen Clinical Concordance Analysis

7.1.1 Targeted Disease Analysis

In addition to traditional sensitivity, specificity and predictive value analysis, the use of likelihood ratio analysis has been recommended for autoimmune testing. Performance of the ANA Screen was compared against five (5) targeted disease associations with results presented in the following table. Samples were prospectively collected from patients being seen in a rheumatology clinic diagnosed using American College of Rheumatology (ACR) or appropriate established disease classification criteria for any mention of the following targeted disease associations:

- Systemic Lupus Erythematosus (SLE)
- Sjögren's Syndrome
- Scleroderma (Systemic Sclerosis)
- Mixed Connective Tissue Disease (MCTD)
- Polymyositis

Table: Targeted Disease Associations

N 908	BioPlex ANA Screen		
	Positive	Negative	Total
Targeted CTD Disease	280	134	414
All Others non targeted and no CTD	110	384	494
Total	390	518	908

Sensitivity	67.6% 95% CI 63.0 -72.3%
Specificity	77.7% 95% CI 73.9 -81.5%
Overall Agreement	73.1% 95% CI 70.2 –76.1%
Positive Likelihood Ratio	3.04 95% CI 2.54 – 3.62
Negative Likelihood Ratio	0.42 95% CI 0.36 – 0.48
Odds Ratio	7.29 95% CI 5.43 – 9.80
Prevalence	45.6% 95% CI 42.3 – 48.9

The above (as well as subsequent) statistical calculations are defined as follows:

Sensitivity: TP/(TP+FN) x 100

Specificity: TN/(FP+TN) x 100

Prevalence: (TP+FN)/(TP+FN+FP+TN) x 100

Overall Agreement: (TP+TN)/(TP+FN+FP+TN) x 100

Positive Likelihood Ratio: Sensitivity/(100-Specificity)

Negative Likelihood Ratio: (100-Sensitivity)/Specificity

Odds Ratio: (TPxTN)/(FPxFN)

Prevalence: (TP+FN)/(TP+FN+FP+TN) x 100

where

TP = True Positive TN True Negative

FP = False Positive FN False Negative

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7.1.2 Individual Disease Analysis

Performance of the ANA Screen was compared against the predicate device in the five (5) targeted disease associations. They are shown in the following set of clinical concordance summary tables where the area(s) in white represent autoantibodies that are clinically relevant for the specific disease classification being discussed. The area(s) in light grey represent autoantibodies that are commonly observed for the specific disease classification. The area(s) in dark grey represent autoantibodies that are not commonly associated with the specific disease classification. Patients may have multiple diagnoses and may be represented in several disease classifications.

Systemic Lupus Erythematosus (SLE)

Performance of the ANA Screen was compared against the predicate device by testing samples prospectively collected from patients being seen in a rheumatology clinic diagnosed using American College of Rheumatology (ACR) criteria for any mention of SLE. The specimens were tested by both the ANA Screen and commercially available microplate EIA methods that were specific for the corresponding autoantibodies. Results are summarized in the following table.

Table: ANA Screen vs EIA: Clinical Diagnosis - SLE

N= 332	ANA Screen	dsDNA [a]	Chromatin	Ribosomal Protein	SS-A	SS-B	Sm	SmRNP	RNP [b]	Scl-70	Jo-1	Centromere B
Bio-Rad and EIA Positive	213	75	86	16	101	34	30	66	53	1	1	6
Bio-Rad Positive and EIA Negative	7	9	36	14	10	8	19	10	13	6	0	5
Bio-Rad and EIA Negative	57	190	183	299	218	280	280	241	244	323	328	321
Bio-Rad Negative and EIA Positive	55	12	27	3	3	10	3	15	7	2	3	0
% Overall Agreement	81%	93%	81%	95%	96%	95%	92%	93%	94%	98%	99%	98%
95% Confidence Interval	77 - 86%	89 - 96%	77 - 85%	92 - 97%	94 - 98%	92 - 97%	90 - 96%	89 - 95%	91 - 97%	96 - 99%	98 - 100%	97 - 100%

Note: 95% confidence interval not calculated for antibodies not clinically relevant to disease.

[a] 46 Bioplex dsDNA indeterminate and EIA dsDNA equivocal results are excluded from the calculations.

[b] 15 EIA RNP equivocal results are excluded from the calculations.

Primary Sjögren's Syndrome

Performance of the ANA Screen was compared against the predicate device by testing samples prospectively collected from patients being seen in a rheumatology clinic diagnosed with an American-European Consensus Group criteria for any mention of Primary Sjögren's Syndrome. The specimens were tested by both the ANA Screen and commercially available microplate EIA methods that were specific for the corresponding autoantibodies. Results are summarized in the following table.

Table: ANA Screen vs EIA: Clinical Diagnosis – Primary Sjögren's Syndrome

N=16	ANA Screen	DsDNA*	Chromatin	Ribosomal Protein	SS-A	SS-B	Sm	SmRNP	RNP	Scl-70	Jo-1	Centromere B
Bio-Rad and EIA Positive	15	1	1	0	15	13	0	0	0	0	0	0
Bio-Rad Positive and EIA Negative	0	0	1	0	0	0	0	0	1	0	0	0
Bio-Rad and EIA Negative	1	12	13	16	1	2	16	14	15	16	16	16
Bio-Rad Negative and EIA Positive	0	0	1	0	0	1	0	2	0	0	0	0
% Overall Agreement	100%	100%	88%	100%	100%	94%	100%	88%	94%	100%	100%	100%
95% Confidence Interval	86 - 100%	51 - 90%	64 - 97%	86 - 100%	86 - 100%	72 - 99%	86 - 100%	64 - 97%	72 - 99%	86 - 100%	86 - 100%	86 - 100%

* 3 dsDNA BioPlex indeterminate and EIA equivocal results were excluded from the calculations.

Scleroderma (Systemic Sclerosis)

Performance of the ANA Screen was compared against the predicate device by testing samples prospectively collected from patients being seen in a rheumatology clinic diagnosed using ACR criteria for any mention of Scleroderma. The specimens were tested by both the ANA Screen and commercially available microplate EIA methods that were specific for the corresponding autoantibodies. Results are summarized in the following table.

Table: ANA Screen vs EIA: Clinical Diagnosis – Scleroderma (Systemic Sclerosis)

N=44	ANA Screen	dsDNA	Chromatin	Ribosomal Protein	SS-A	SS-B	Sm	SmRNP	RNP	Scl-70	Jo-1	Centromere B
Bio-Rad and EIA Positive	28	1	3	0	7	1	0	3	4	6	0	12
Bio-Rad Positive and EIA Negative	1	3	3	0	3	1	2	0	0	1	0	0
Bio-Rad and EIA Negative	5	40	36	44	30	42	42	40	38	36	44	32
Bio-Rad Negative and EIA Positive	10	0	2	0	4	0	0	1	2	1	0	0
% Overall Agreement	75%	93%	89%	100%	84%	98%	96%	98%	96%	96%	100%	100%
95% Confidence Interval	60 - 90%	84 - 100%	78 - 100%	99 - 100%	72 - 97%	92 - 100%	88 - 100%	92 - 100%	88 - 100%	87 - 100%	99 - 100%	99 - 100%

Mixed Connective Tissue Disease (MCTD)

Performance of the ANA Screen was compared against the predicate device by testing samples prospectively collected from patients seen in a rheumatology clinic who were diagnosed with an Alaracon-Segovia or Kahn criteria for any mention of MCTD. The specimens were tested by both the ANA Screen and commercially available microplate EIA methods that were specific for the corresponding autoantibodies. The high incidence of anti-chromatin antibodies in patients with MCTD has been previously documented. Results are summarized in the following table.

Table: ANA Screen vs EIA: Clinical Diagnosis – Mixed Connective Tissue Disease (MCTD)

N=16	ANA Screen	dsDNA	Chromatin	Ribosomal Protein	SS-A	SS-B	Sm	SmRNP	RNP	Scl-70	Jo-1	Centromere B
Bio-Rad and EIA Positive	16	1	3	1	2	0	4	15	14	0	1	1
Bio-Rad Positive and EIA Negative	0	1	11	0	0	0	1	0	1	1	0	0
Bio-Rad and EIA Negative	0	13	2	15	14	16	10	1	1	15	15	15
Bio-Rad Negative and EIA Positive	0	1	0	0	0	0	1	0	0	0	0	0
% Overall Agreement	100%	88%	31%	100%	100%	100%	88%	100%	94%	94%	100%	100%
95% Confidence Interval	86 - 100%	64 - 97%	14 - 56%	86 - 100%	86 - 100%	86 - 100%	64 - 97%	86 - 100%	72 - 99%	72 - 99%	86 - 100%	86 - 100%

Polymyositis

Performance of the ANA Screen was compared against the predicate device by testing samples prospectively collected from patients seen in a rheumatology clinic who were diagnosed with literature criteria for Polymyositis. The specimens were tested by both the ANA Screen and commercially available microplate EIA methods that were specific for the corresponding autoantibodies. Note: The presence of antibodies to Jo-1 in patients diagnosed with Polymyositis has been well documented. Results are summarized in the following table.

Table: ANA Screen vs EIA: Clinical Diagnosis – Polymyositis

N=12	ANA Screen	dsDNA	Chromatin	Ribosomal Protein	SS-A	SS-B	Sm	SmRNP	RNP	Scl-70	Jo-1	Centromere B
Bio-Rad and EIA Positive	6	0	0	0	5	0	0	1	1	0	2	0
Bio-Rad Positive and EIA Negative	0	0	1	0	0	0	0	0	0	0	0	0
Bio-Rad and EIA Negative	3	12	11	12	7	12	12	11	11	12	10	12
Bio-Rad Negative and EIA Positive	3	0	0	0	0	0	0	0	0	0	0	0
% Overall Agreement	75%	100%	92%	100%	100%	100%	100%	100%	100%	100%	100%	100%
95% Confidence Interval	47 - 91%	82 - 100%	65 - 99%	82 - 100%	82 - 100%	82 - 100%	82 - 100%	82 - 100%	82 - 100%	82 - 100%	82 - 100%	82 - 100%

Non-Targeted and No Connective Tissue Disease

Performance of the ANA Screen was compared against the predicate device by testing samples prospectively collected from patients seen in a rheumatology clinic who were not diagnosed with a targeted connective tissue disease by established medical criteria. The specimens were tested by both the ANA Screen and commercially available microplate EIA methods that were specific for the corresponding autoantibodies. Results are summarized in the following table.

Table: ANA Screen vs EIA: Clinical Diagnosis - Non-Targeted and No Connective Tissue Disease

N=494	ANA Screen	dsDNA	Chromatin	Ribosomal Protein	SS-A	SS-B	Sm	SmRNP	RNP	Scl-70	Jo-1	Centromere B
BioPlex 2200 and EIA Positive	79	6	7	1	28	9	3	9	10	2	2	13
BioPlex 2200 Positive and EIA Negative	31	15	20	5	6	10	4	3	12	6	0	1
BioPlex 2200 and EIA Negative	303	459	437	488	453	474	486	477	465	481	490	479
BioPlex 2200 Negative and EIA Positive	81	14	30	0	7	1	1	5	7	5	2	1
% Overall Agreement	77%	94%	90%	99%	97%	98%	99%	98%	96%	98%	99.6%	99.6%
95% Confidence Interval	74-81%	92-96%	87-93%	98-100%	96-99%	96-99%	98-100%	97-100%	94-98%	96-99%	99-100%	99-100%

7.2 MEDICAL DECISION SUPPORT SOFTWARE (MDSS) PERFORMANCE ANALYSIS

BioPlex ANA Screen Medical Decision Support Software (MDSS) results, when compared with disease classification by ACR, literature or appropriate established medical criteria for targeted connective tissue disease (TCTD), are presented in the following tables. The MDSS can suggest one or more possible disease associations after identifying patterns from the eleven (11) individual antibody results. Suggesting one or more possible disease associations may aid a physician in the differential diagnosis of certain systemic autoimmune diseases, since a recent study demonstrated only a 49% agreement between the referring and final diagnosis. In addition, MDSS can report that antibody levels show no association with MDSS defined patterns (No Association), or may report that all antibody results are below the established cut-offs (Negative). A total of 1,130 results, a combination of the 908 subjects seen in rheumatology clinics and the 222 normal blood donors presumed to be negative for autoimmune diseases, were analyzed.

Note: It is sometimes difficult to distinguish SLE and Sjögren's disease, even when both serological and clinical data are considered. The complexity inherent in diagnosing autoimmune disease is further illustrated in a recent study that demonstrated only a 49% agreement between the referring physician and final diagnosis.

MDSS descriptions used in the following MDSS clinical performance tables are defined as follows:

Negative for all antibodies	All antibody levels for systemic autoimmune disease are below pre-established cutoffs
Positive for one or more antibody	Any one of the BioPlex 2200 ANA 11 analytes is positive
SLE	Systemic Lupus Erythematosus
SS	Sjögren's Syndrome
Scleroderma	same
MCTD	Mixed Connective Tissue Disease
Polymyositis	same
No Association	Antibody levels show no association with MDSS defined patterns for systemic autoimmune diseases

7.2.1 MDSS vs. Disease Classification – Targeted and Non-Targeted Connective Tissue Diseases

The following table presents percent disease agreement of the MDSS output with the diagnosis provided by a physician. Data is presented as percent diseases agreement for patients with one or more positive antibodies and for patients with a targeted connective tissue disease (TCTD) classification, regardless of antibody response. The difference between disease agreements is the inclusion of negative results for all antibodies in the TCTD patients. MDSS does not provide an association with a patient with negative test results for all antibodies.

Table: MDSS vs. Disease Classification (N=1130)

Disease Classification by Criteria**		(N)	Negative for all antibodies	Positive for one or more antibody (P)	MDSS Output *						% Disease Agreement	
					No Association	Any SLE Association	Any Sjögren's Syndrome Association	Any SclCR Association	Any MCTD Association	Any Polymyositis Association	Patients with Positive Antibody Only (P)	Patients with TCTD Classification (N)
Targeted Connective Tissue Disease (TCTD)	Systemic Lupus Erythematosus (SLE)	332	114	218	28	186	22	7	18	0	85.3% (186/218)	56.0% (186/332)
	Primary Sjögren's Syndrome	16	1	15	0	15	13	0	0	0	86.7% (13/15)	81.3% (13/16)
	Scleroderma	44	13	31	3	19	1	16	3	0	51.6% (16/31)	36.4% (16/44)
	Mixed Connective Tissue Disease (MCTD)	16	0	16	0	15	0	1	13	0	81.3% (13/16)	81.3% (13/16)
	Polymyositis	12	6	6	0	4	0	0	1	2***	33.3% (2/6)	16.7% (2/12)

* *See Appendix A for a complete list of possible MDSS outputs. Note: as indicated in Appendix A, not all MDSS outputs were observed in the clinical trial. Sjögren's Syndrome alone and MCTD alone are not outputs of MDSS.*

***Targeted diseases presented include all patients with each disease classification, and patients may have multiple disease classifications, with the exception of Primary Sjögren's Syndrome.*

****For these patients, the MDSS outputs suggesting Polymyositis referenced the disorder alone and not in combination with another Targeted Connective Tissue Disease.*

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7.2.2 MDSS Assignments in Patients with TCTD and a Positive Antibody Result

Laboratory measurement of autoantibodies has historically been driven by a presumptive diagnosis. For example, a request for anti-Sm would follow from a presumptive diagnosis of SLE. A positive result for anti-Sm would be supportive of the presumptive diagnosis. The table below presents the % agreement of the MDSS output when a specific positive antibody result is present and the diagnosis provided by the physician is consistent with the presence of that antibody. The table shows that for such samples, the MDSS associations are in good agreement with the diagnosis by established medical criteria.

Table: MDSS Assignments in Patients with TCTD and a Positive Antibody Result

Positive Antibody Test Results	Disease by Established Medical Criteria*	MDSS Output**	% Agreement	95% Confidence Interval
dsDNA (N = 119)	SLE (N = 92)	Any SLE (N = 87)	87/92 or 95%	89-100%
Chromatin (N = 168)	SLE (N = 122)	Any SLE (N = 112)	112/122 or 92%	86-97%
Ribosomal Protein (N = 37)	SLE (N = 30)	Any SLE (N = 29)	29/30 or 97%	83-99%
SSA (N = 173)	SS (N = 15)	SS or SLE (N = 13)	13/15 or 87%	62-96%
	SLE (N = 111)	Any SLE (N = 106)	106/111 or 96%	91-100%
SSB (N 76)	SS (N 13)	SS or SLE (N = 13)	13/13 or 100%	83-100%
Sm (N 60)	SLE (N = 49)	Any SLE (N = 49)	49/49 or 100%	99-100%
SmRNP (N = 103)	MCTD (N = 15)	MCTD or SLE (N = 13)	13/15 or 87%	62-96%
RNP (N = 112)	MCTD (N = 15)	MCTD or SLE (N = 13)	13/15 or 87%	62-96%
Scl-70 (N = 23)	Scleroderma (N = 7)	Scleroderma; SLE or Scleroderma (N 5)	5/7 or 71%	36-92%
Jo-1 (N = 6)***	Polymyositis (N = 2)	Polymyositis (N = 2)	2/2 or 100%	43-100%
Centromere (N = 38)	Scleroderma (N = 12)	Scleroderma; SLE or Scleroderma (N = 11)	11/12 or 92%	65-99%
	SLE (N = 11)	Any SLE (N = 9)	9/11 or 82%	52-95%

* *Targeted diseases presented include all patients with each disease classification, and patients may have multiple disease classifications. Established medical criteria used in this study include criteria established by the American College of Rheumatology (ACR), American-European Consensus Group, Alarcon-Segovia or Kahn, as well as literature criteria for Polymyositis.*

***See Appendix A of the Instructions For Use for a complete list of possible MDSS outputs.*

****Note: The presence of antibodies to Jo-1 in patients diagnosed with Polymyositis has been well documented*

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7.2.3 MDSS Agreement with Disease Classification by Criteria

For each of the targeted connective tissue diseases encountered in the clinical trial, the tables below present the number of patients with a positive antibody test and the number of correct MDSS associations in addition to calculations of Odds Ratio, Positive Likelihood Ratio, and Negative Likelihood Ratio. Since some MDSS outputs contain more disease associations than the disease association under consideration, the results in the first table were calculated by excluding patients with other diseases listed in the output. The second table presents results where these patients were not excluded. Not all patients with a targeted connective tissue disease produce antibodies that may be detected with the BioPlex 2200 ANA Screen.

Table: MDSS Agreement with Disease Classification (excluding patients with other MDSS associations)

Disease Classification by Criteria	Systemic Lupus Erythematosus (SLE) (N = 332)	Primary Sjögren's Syndrome (N = 16)	Scleroderma (N = 44)	Mixed Connective Tissue Disease (N = 16)	Polymyositis (N = 12)
Positive Antibody Test(s)	218	15	31	16	6
MDSS Associations	186	13	16	13	2
Odds Ratio (OR)	12.8	479.8	22.1	481	223.4
OR 95% Confidence Interval	9.1 - 17.8	111.4 - 2065.6	10.3 - 47.5	111.7 - 2071.9	11.9 - 2667.6
Positive Likelihood Ratio (PLR)	6.17	90.8	14.4	91.0	186.3
(PLR) 95% Confidence Interval	4.8 - 7.9	41.8 - 196.9	7.9 - 26.1	41.95 - 197.35	18.1 - 1919.2
Negative Likelihood Ratio (NLR)	0.48	0.19	0.65	0.19	0.83
NLR 95% Confidence Interval	0.43 - 0.54	0.07 - 0.52	0.52 - 0.81	0.07 - 0.52	0.65 - 1.07
Total N after exclusions	1059	798	798	800	1130

Table: MDSS Agreement with Disease Classification (including patients with multiple MDSS associations)

Disease Classification by Criteria	Systemic Lupus Erythematosus (SLE) (N = 332)	Primary Sjögren's Syndrome (N = 16)	Scleroderma (N = 44)	Mixed Connective Tissue Disease (N = 16)	Polymyositis (N = 12)
Positive Antibody Test(s)	218	15	31	16	6
MDSS Associations	186	13	16	13	2
Odds Ratio (OR)	7.9	162.1	23.3	196.8	223.4
OR 95% Confidence Interval	5.9 - 10.6	43.8 - 599.6	11.3 - 48.2	52.6 - 735.4	11.9 - 2667.6
Positive Likelihood Ratio (PLR)	4.03	31.21	15.19	37.71	186.3
(PLR) 95% Confidence Interval	3.3 - 4.9	20.3 - 47.9	8.8 - 26.2	23.8 - 59.8	18.1 - 1919.2
Negative Likelihood Ratio (NLR)	0.51	0.19	0.65	0.19	0.83
NLR 95% Confidence Interval	0.45 - 0.57	0.07 - 0.53	0.52 - 0.81	0.07 - 0.53	0.65 - 1.07
Total N	1130	1130	1130	1130	1130

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7.2.4 MDSS vs. Non-Targeted Connective Tissue Diseases

Some of the Clinical Disease Classifications encountered do not have an associated MDSS output. These non-targeted connective tissue diseases should be classified as either Negative or No Association by MDSS. However, in some instances, a MDSS association was incorrectly presented. The MDSS results incorrectly associated with a targeted connective tissue disease can be classified as % Incorrect Association. The results are summarized in the following table:

Table: MDSS vs. Non-Targeted Connective Tissue Diseases

Clinical Disease Classification		(N)	Negative or No MDSS Associations	Incorrect MDSS Associations	% Incorrect Association
Non TCTD	Dermatomyositis- only	15	12	3	20% (3/15)
	Rheumatoid Arthritis- only	341	310	31*	9% (31/341)
	Other CTD- only	45	36	9	20% (9/45)
No CTD		77	77	61	16
Blood Donor Samples		222	222	214	8**

* *Of the 31 patients with only rheumatoid arthritis, 27 were associated with SLE by MDSS.* ***Patients with Rheumatoid Arthritis may result in an SLE association from MDSS.*** *Additionally, patients with Rheumatoid Arthritis who are receiving anti-TNFα blockers as part of their therapy have been reported to produce antibodies against both dsDNA and Chromatin. For these reasons, MDSS associations from patients with Rheumatoid Arthritis should be interpreted with caution. See also Limitations of the Procedure.*

** *The clinical status of blood donors tested in this study was not known.*

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7.2.5 MDSS Correct Association with Disease Classification

Traditional evaluation strategies for diagnostic tests do not always directly apply to the evaluation of decision support systems, because decision support systems often do not provide one answer, and each subject may have more than one diagnosis. The percent correctness is defined for this study as the number of patients with a given MDSS association who also have that disease by ACR, literature, or established medical criteria. The percent correctness results illustrated in Tables T and U should be considered in conjunction with the following prevalence of disease observed in this study: SLE 29% (332/1130), Sjögren's Syndrome 1.4% (16/1130), Scleroderma 3.9% (44/1130), Mixed Connective Tissue Disease 1.4% (16/1130), Polymyositis 1.1% (12/1130), Other Connective Tissue Disease 36.9% (417/1130), and No Connective Tissue Disease 6.8% (77/1130). Note: the Correct Association values presented in the following tables may change in different patient populations.

Table: Correct Association without any Targeted Disease Classification

MDSS Output	# by MDSS	# Without any Targeted Disease	Correct Association	95% Confidence Interval
Negative	719	585	81.4% (585/719)	78.4 - 84.3%
No Association	89	57	64% (57/89)	53.3 - 74.8

Table: Correct Association with Targeted Disease Classification

MDSS Output	# by MDSS	# by Clinical Diagnosis	Correct Association	95% Confidence Interval
SLE only	198	142	71.7% (142/198)	65.1 - 78.3%
SLE or SS	42	35	83.3% (35/42)	70.2 - 96.5%
MCTD or SLE	37	30	81.1% (30/37)	66.3 - 95.9%
Scleroderma	22	9	40.9% (9/22)	23.3 - 61.3%
SLE or Scleroderma	20	11	55% (11/20)	34.2 - 74.2%
Polymyositis only	3*	2	66.7% (2/3)	20.8 - 93.9%

* One of these 3 patients was diagnosed with Dermatomyositis.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

OCT 27 2005

Bio-Rad Laboratories
c/o Mr. Christopher Bentsen
Manager, Regulatory, Quality and Clinical Affairs
6565 185th Ave., NE
Redmond, WA 98052

Re: k043341
Trade/Device Name: BioPlex™ 2200 ANA Screen with Medical Decision Support Software (MDSS) for use with the BioPlex™ 2200 Multi-Analyte Detection System
Regulation Number: 21 CFR 862.3100
Regulation Name: Liquid Chromatography, Amphetamine
Regulatory Class: Class II
Product Code: NVI
Dated: December 2, 2004
Received: December 3, 2004

Dear Mr. Bentsen:

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.

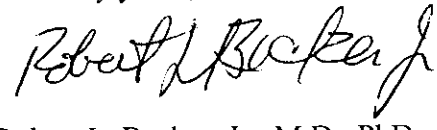
If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish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

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (240) 276-0131. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). 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) 443-6597 or at its Internet address
http://www.fda.gov/cdrh/dsma/dsmamain.html

Sincerely yours,



Robert L. Becker, Jr., M.D., PhD
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

INDICATIONS FOR USE STATEMENT

510(k) Number (if known): K043341

Device Name: BioPlex™ 2200 ANA Screen with Medical Decision Support Software (MDSS) for use with the BioPlex™ 2200 Multi-Analyte Detection System

Indications for Use:

The BioPlex™ 2200 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, SmRNP, RNP, Scl-70, Jo-1, and Centromere B) in human serum and/or EDTA or heparinized plasma.

The ANA Screen is used to screen serum or plasma (EDTA, heparin) samples and detect the presence of antinuclear antibodies as an aid in the diagnosis of systemic autoimmune diseases (Systemic Lupus Erythematosus [SLE], Mixed Connective Tissue Disease [MCTD], Undifferentiated Connective Tissue Disease [UCTD], Sjögren's Syndrome [SS], Scleroderma [Systemic Sclerosis], Dermatomyositis, Polymyositis, Rheumatoid Arthritis [RA], CREST Syndrome, and Raynaud's Phenomenon) in conjunction with clinical findings and other laboratory tests.

The ANA Screen is intended for use with the Bio-Rad BioPlex 2200 System.

The BioPlex 2200 Medical Decision Support Software (MDSS), used in conjunction with the ANA Screen, is an optional laboratory tool that associates patient antibody results from the ANA Screen with predefined MDSS profiles that have been correlated with the following systemic autoimmune diseases: Systemic Lupus Erythematosus (SLE), Mixed Connective Tissue Disease (MCTD), Sjögren's Syndrome (SS), Scleroderma (Systemic Sclerosis) and Polymyositis.

Prescription Use: ___X___ (Per 21 CFR 801.109) AND/OR Over-The-Counter Use: _____ (Optional Format 1-2-96)

(PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Maria Chan
Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

510(k) K043341