2/16/99

K981831

510k Summary of Safety and Effectiveness

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.

The assigned 510(k) number is: K981831

Applicant Information:

Date Prepared:	May 18, 1998
Name:	Columbia Bioscience, Inc.
Address:	8775 M Centre Park Drive, #559 Columbia, MD 21045
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Device Information:

Trade Name:	IS EBV EA-D IgG ELISA Kit
Common Name:	EBV Early Antigen EIA Test
Classification Name;	Epstein Barr Virus Serological Reagent

Equivalent Device Description:
Wampole EA-D IgG ELISA.
Wampole EA-D IgG ELISA kit contains instructions and materials for the qualitative and semi-quantitative detection of IgG antibodies to EBV-EA-D IgG in human serum by indirect ELISA

Device Description: The IS EBV-EA-D IgG ELISA Kit is an enzyme-linked immunosorbent assay (ELISA) for the detection of IgG to Epstein Barr Early Antigen diffuse in human serum.

Intended Use: For the qualitative and semi-quantitative determination of IgG antibodies to Epstein-Barr Virus (recombinant) Early Antigen Diffuse (EBV-EA-D IgG) in human serum by indirect enzyme immunoassay. The Is-EBV-EA-D IgG Test Kit may be used in combination with other Epstein-Barr serologies (Viral Capsid Antigen (VCA) IgG and IgM , Epstein-Barr Nuclear Antigen-1 (EA-D) IgG and IgM, Early Antigen-Diffuse (EA-D) IgM and heterophile antibody as an aid in the diagnosis of infectious mononucleosis (IM). The evaluation of paired sera, to deter-mine a significant increase in EA-D IgG antibody titer, can also aid in the diagnosis of acute infection. These reagents can be used either manually or in conjunction with the MAGO® Plus Automated Processor.

Principle of Procedure:
Recombinant EA-D antigen is bound to microwells. Diluted patient sera, Cut-Off Calibrator and controls are placed inthe microwells and incubated. Anti-EA-D IgG antibodes, if present, will bind to the antigen forming antigen-antibody complexes. Residual sample is eliminated by aspirating and washing. Conjugate (horseradish peroxidase-labeled anti-human IgG) is added and will bind to these complexes. Unbound conjugate is removed by aspiration and washing. Substrate is then added and incubated. In the presence of bound enzyme the substrate is converted to an end product. The absorbance of this end product can be read spectrophotometrically at 450 nm (reference 600-630 nm) and is directly proportional to the concentration of IgG antibodies to EA-D present in the sample.

The Is-EBV-EA-D IgG ELISA kit and the Wampole EA-D IgG ELISA are substantially equivalent in that:

1. Both are *in vitro* immunologic methods.
2. Both are intended for use in the detection of IgG antibody to EBV-EA-D in human serum
3. Both are based on the formation of a complex between EA-D antigens and antibody
4. Both use antigen coated microtiter plates.
5. Both use goat anti-human IgG conjugated to horseradish peroxidase.
6. Both use TMB as the enzyme substrate.

A detailed comparison between the proposed devise and the predicate device is shown in Table 1.

Conclusions: The Diamedix Is-EBV-EA-D IgG is substantially equivalent to the Wampole EA-D ELISA for the detection of IgG antibodies to EBV-EA-D in human serum to aid in the diagnosis of infectious mononucleosis. The device is as safe, as effective, and performs as well as the legally marketed device described.

Table 1

	PROPOSED DEVICE **Diamedix Is-EBV-EA-D IgG ELISA Kit**	**PREDICATE DEVICE** **Wampole EA-D IgG ELISA**
Intended Use	For the qualitative and semi-quantitative determination of IgG antibodies to Epstein-Barr Virus (recombinant) Early Antigen Diffuse (EBV-EA-D IgG) in human serum by indirect enzyme immunoassay. The Is-EBV-EA-D IgG Test Kit may be used in combination with other Epstein-Barr serologies (Viral Capsid Antigen (VCA) IgG and IgM , Epstein-Barr Nuclear Antigen-1 (EA-D) IgG and IgM, Early Antigen-Diffuse (EA-D) IgM and heterophile antibody as an aid in the diagnosis of infectious mononucleosis (IM). The evaluation of paired sera, to determine a significant increase in EA-D IgG antibody titer, can also aid in the diagnosis of acute infection. These reagents can be used either manually or in conjunction with the MAGO® Plus Automated Processor.	The Epstein-Barr Early Antigen Diffuse component (EA-D) IgG kit is an Enzyme-Linked ImmunoSorbent Assay (ELISA) for the qualitative determination of IgG antibodies in human serum to EA-D antigen. The Wampole anti-EA-D assay may be used in conjunction with other Epstein-Barr serologies (VCA IgG, VCA IgM, EBNA-1 IgG, EBNA-1 IgM, and heterophile) as an aid in the diagnosis of infectious mononucleosis.
Methodology	Enzyme immunoassay (EIA)	Enzyme Linked Immunosorbent Assay (ELISA)
Specifications	For *in vitro* diagnostic use. For use with fresh or frozen human serum. Avoid lipemic, hemolyzed, contaminated, or icteric sera. Assay performed on 1:21 dilution of serum at 18-30°C. Store at 2-8°C.	For *in vitro* diagnostic use. For use with fresh or frzen human serum. Assay performed on 1:21 dilution of serum at 21-25°C. Store at 2-8°C.
Design	Is-EBV-EA-D IgG Test Kit. 96 determinations. Un-diluted Calibrator, Positive, and Negative controls.	EA-D IgG ELISA. 96 determinations. Undiluted Calibrator, High positive, Low positive, and Negative controls.
Principles of Operation	Purified, recombinant EA-D antigen is bound to microwells (solid phase). Diluted human serum is asses to the microwell which binds human anti-EA-D IgG, if present. Solid phase is washed and exposed to anti-human IgG conjugate. Solid phase is washed and exposed to enzyme substrate to develop color. Strong acid is added to stop reaction. The color is read at 450/600 nm on an EIA reader.	Diluted patient serum is incubated with purified, recombinant EA-D antigen bound to the solid surface of a microtiter well. If IgG antibodies against EBV-EA-D are present in the serum, antigen-antibody complexes are formed. These complexes bind with HRP-labeled anti-human IgG which react with the addition of chromogen, resulting in a color development. The absorbance is measured at 450/630 nm.
Performance Characteristics	Relative Sensitivity (Late Infection): 81.8% Relative Sensitivity (Current Infection): 28.1% Relative Specificity (Convalescent): 89.7% Relative Specificity (Seronegative): 100.0% Agreement: 79.9% Intra-assay Precision (Positive samples, all sites) Overall Manual- 2.07-13.88 MAGO Plus- 1.77-18.00 Interassay Precision (Positive samples, all sites) Overall Manual- 5.12-9.08 MAGO Plus- 5.09-11.61 No Cross-reactivity	Relative Sensitivity (Late Acute): 100.0% Relative Specificity (Seronegative): 100.0% Relative Specificity (Early Acute): 97.0% Relative Sensitivity (Seropositive): 19.7% Relative Specificity (Seropositive): 80.3% Agreement: 85.6% Inter-Site Precision (Positive samples, all sites) Overall: 5.96-8.83% No Cross-reactivity
Enzyme Used	Horesradish Peroxidase	Horesradish Peroxidase
Substrate	TMB	TMB
Specimen	Serum	Serum
Calculation of Results	Sample Absorbance/Cut-off Absorbance = Index Value	Sample Absorbance/Cut-off Absorbance = ISR
Interpretation	<0.90 Negative 0.91-1.09 Equivocal ≥1.10 Positive	≤0.90 Negative for EA-D IgG 0.91-1.09 Equivocal for EA-D IgG ≥ 1.10 Positive for EA-D IgG
Materials	96 microwells in 12x8 strips, Wash concentrate, Sample Diluent, Conjugate, Calibrator, Controls, Substrate, Stop Solution	96 microwells in 12x8 strips, Wash Buffer, Serum Diluent, HRP Conjugate, Calibrator, Controls, Chromogen, Stop Solution.

Performance Characteristics

A. Clinical Sensitivity and Specificity Using Characterized Sera

Frozen retrospective sera from one hundred and eighty four patients were characterized using commercially available kits for VCA IgG, VCA IgM, EBNA IgG and heterophile antibodies. Based on the results of this testing, the patient sera were characterized as follows :

- 102 sera were characterized as past infection. These were positive for VCA IgG and/or EBNA IgG antibodies and negative for VCA IgM and heterophile antibody.
- 34 sera were characterized as seronegative. These were negative for VCA IgG, VCA IgM, EBNA IgG and heterophile antibody.
- 37 sera were characterized as having a current (recent) infection. These were positive for VCA IgM and/or heterophile antibody and were negative for EBNA IgG.
- 11 sera were characterized as having a transitional infection. These were positive for VCA IgM and/or heterophile antibody and were positive for EBNA IgG.

All 184 sera were then tested by an independent clinical commercial laboratory using the Is-EBV-EA-D IgG Test Kit. The results obtained are shown in Table 2:

EBV Serological Status

TABLE 2	*Past Infection*	*Current Infection*	*Transitional*	*Seronegative*
Is-EBV-EA-D IgG POSITIVE	10	9	9	0
NEGATIVE	87	23	2	34
*EQUIVOCAL	5	5	0	0

- Of the 102 past infection sera tested, 87 were negative for anti-EA-D IgG, ten were positive, and five were equivocal.
- Of the thirty-seven current (recent) infection samples tested, twenty-three were negative for anti-EA-D IgG, nine were positive, and five were equivocal.
- Of the eleven transitional infection sera tested, nine were positive for EAD IgG and two were negative.
- Of the thirty-four seronegative sera tested, thirty-four were negative for anti-EA-D IgG.
- The overall agreement of the Is-EBV-EA-D IgG test kit compared to EBV serological status was 139/174 = 79.9%.

B. Precision

To determine the precision of the Is-EBV-EA-D IgG Test Kit, four positive and two negative sera were assayed ten times each in three different runs at three different sites. The intra- and interassay precision obtained at each site is shown in Tables 3, 4 and 5.

TABLE 3 : Site #1 - Intra-Assay and Interassay Precision

SERUM	INTRA-ASSAY RUN 1 MEAN INDEX	CV%	INTRA-ASSAY RUN 2 MEAN INDEX	CV%	INTRA-ASSAY RUN 3 MEAN INDEX	CV%	INTERASSAY MEAN INDEX	CV%	
A (POS)	1.88	4.97	1.79	5.61	1.77	6.28	1.81	6.03	
B (POS)	2.55	6.77	2.42	5.11	2.25	6.54	2.41	7.87	
C (POS)	2.21	6.87	2.18	4.76	2.02	4.26	2.14	6.59	
D (POS)	1.17	5.11	1.17	13.88	1.15	6.49	1.16	9.08	
E (NEG)	0.18	13.02	0.16	30.06	0.16	18.13	0.17	21.00	
F (NEG)	0.27	10.26	0.27	11.97	0.28	15.93	0.27	12.87	
						CAL	0.97	12.06	n = 9
						PC	1.53	4.89	n = 3
						NC	0.30	5.04	n = 3

TABLE 4 : Site #2- Intra-Assay and Interassay Precision

SERUM	INTRA-ASSAY RUN 1 MEAN INDEX	CV%	INTRA-ASSAY RUN 2 MEAN INDEX	CV%	INTRA-ASSAY RUN 3 MEAN INDEX	CV%	INTERASSAY MEAN INDEX	CV%	
A (POS)	1.77	5.18	1.84	2.07	1.70	3.99	1.77	5.12	
B (POS)	2.54	4.41	2.60	3.75	2.28	2.83	2.47	6.73	
C (POS)	2.27	5.41	2.32	4.62	2.05	4.34	2.21	7.08	
D (POS)	1.34	3.70	1.23	4.24	1.16	3.45	1.24	7.23	
E (NEG)	0.23	6.31	0.22	5.98	0.20	5.43	0.22	7.79	
F (NEG)	0.34	5.60	0.30	6.71	0.31	9.76	0.32	8.91	
						CAL	1.00	4.77	n = 18
						PC	1.62	4.49	n = 12
						NC	0.36	12.16	n = 12

TABLE 5 : Site #3 - Intra-assay and Interassay Precision

SERUM	INTRA-ASSAY RUN 1 MEAN INDEX	CV%	INTRA-ASSAY RUN 2 MEAN INDEX	CV%	INTRA-ASSAY RUN 3 MEAN INDEX	CV%	INTERASSAY MEAN INDEX	CV%	
A (POS)	1.78	6.98	1.70	2.68	1.86	4.15	1.78	6.05	
B (POS)	2.42	4.47	2.57	3.77	2.66	3.01	2.55	5.32	
C (POS)	2.15	3.05	2.19	5.29	2.33	3.86	2.22	5.39	
D (POS)	1.13	6.81	1.12	5.78	1.13	7.23	1.12	6.43	
E (NEG)	0.18	10.78	0.20	11.33	0.19	10.23	0.19	11.38	
F (NEG)	0.28	8.75	0.34	37.55	0.32	11.78	0.31	25.10	
						CAL	1.00	2.60	n = 9
						PC	1.54	12.50	n = 3
						NC	0.32	2.60	n = 3

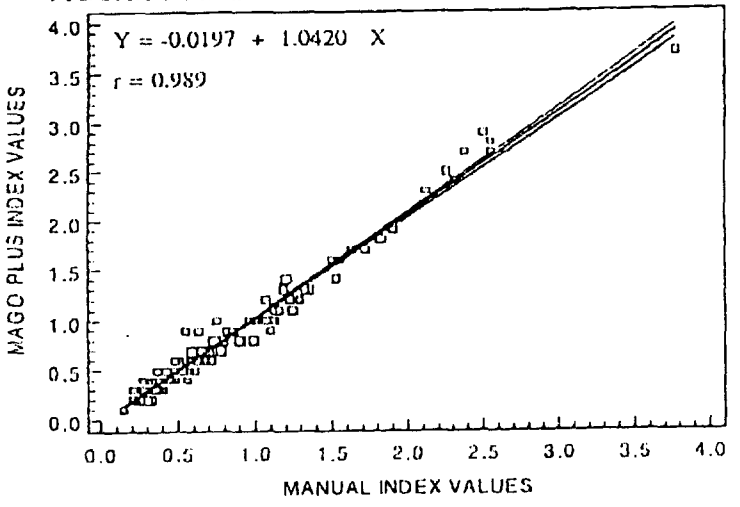
C. Specificity with Potentially Cross-Reactive Sera

Sixteen sera, non-reactive (negative) for IgG antibodies to EA-D in the Is-EBV-EA-D IgG Test Kit, were tested by EIA for IgG antibody to varicella zoster, cytomegalovirus and herpes simplex virus. 15/15 anti-VZV IgG positive sera were non-reactive for anti-EA-D IgG; 3/3 anti-CMV IgG positive sera were non-reactive for anti-EA-D IgG and 3/3 anti-HSV positive sera were non-reactive for anti-EA-D IgG. This suggests that no specific cross-reactivity should be expected with the Is-EBV-EA-D IgG Test Kit from these analytes.

D. Correlation of Manual and MAGO Plus Results

The Is-EBV-EA-D IgG Test Kit has been developed for automated as well as manual use. To demonstrate the equivalence of the manual and MAGO Plus procedures, the results of 193 serum samples tested by both methods were plotted. A scattergram and regression line of the results obtained with 95% confidence intervals is shown in Figure 3. The data indicate good correlation with a Pearson Correlation Coefficient of 0.989.

FIGURE 3 : Manual and MAGO Plus Result Correlation



D. MAGO Plus Precision

The precision of the assay when performed on the MAGO Plus Automated EIA Processor was determined by assaying six sera ten times each in three different runs. Table 6 shows the intra-and interassay precision obtained using the MAGO Plus.

TABLE 6 : **Site #2- Intra-Assay and Interassay Precision - MAGO Plus**

SERUM	INTRA-ASSAY RUN 1		INTRA-ASSAY RUN 2		INTRA-ASSAY RUN 3		INTERASSAY		
	MEAN INDEX	CV%	MEAN INDEX	CV%	MEAN INDEX	CV%	MEAN INDEX	CV%	
A (POS)	1.79	1.77	1.98	2.13	1.84	3.80	1.87	5.09	
B (POS)	2.30	2.90	2.59	2.85	2.40	3.40	2.43	5.83	
C (POS)	2.15	3.95	2.35	3.01	2.13	3.87	2.21	5.74	
D (POS)	1.20	18.00	1.35	5.24	1.25	5.66	1.27	11.61	
E (NEG)	0.20	0.00	0.24	21.52	0.20	0.00	0.21	16.21	
F (NEG)	0.33	20.45	0.37	18.24	0.31	18.31	0.34	19.86	
						CAL	0.99	5.35	n = 9
						PC	1.50	0.00	n = 3
						NC	0.33	17.32	n = 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

FEB 16 1999

Diamedix Corporation
c/o Norman Jenkins
Columbia Bioscience, Inc.
8775 M Centre Park Drive, #559
Columbia, MD 21045

Re: K981831
Trade Name: Is EBV-EA-D IgG ELISA Test System
Regulatory Class: I
Product Code: GNP
Dated: December 14, 1998
Received: December 14, 1998

Dear Mr. Jenkins:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we 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). 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 (Premarket Approval), 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 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770)488-7655.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a 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 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll free number (800) 638-2041 or at (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsmamain.html"

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number: K981831

Device Name: EBV- EA-D IgG ELISA

Indications For Use: For the qualitative and semi-quantitative determination of IgG antibodies to Epstein-Barr Virus (recombinant) Early Antigen Diffuse (EBV-EA-D IgG) in human serum by indirect enzyme immunoassay. The Is-EBV-EA-D IgG Test Kit may be used in combination with other Epstein-Barr serologies (Viral Capsid Antigen (VCA) IgG and IgM , Epstein-Barr Nuclear Antigen-1 (EBNA-1) IgG and IgM, Early Antigen-Diffuse (EA-D) IgM and heterophile antibody as an aid in the diagnosis of infectious mononucleosis (IM). The evaluation of paired sera, to determine a significant increase in EA-D IgG antibody titer, can also aid in the diagnosis of acute infection. These reagents can be used either manually or in conjunction with the MAGO® Plus Automated Processor.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use X (Per 21 CFR 801.109) OR Over-The Counter Use ____ (Optional Format 1-2-96)

Woody Dubois

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K981831