K983841

JUN 9 1999

ATTACHMENT I

REVISED 510(k) SUMMARY

510(k) Summary of Information Respecting Safety and Effectiveness

A. Name and Address of Submitter

Company Name and Address:	Biotest Diagnostics Corporation 66 Ford Road, Suite 131 Denville, NJ 07834
Telephone:	(609) 397-8511
FAX:	(609) 397-8224
Contact Person:	Patricia E. Bonness, Official Correspondent

Date 510(k) Summary was Prepared: October 26, 1998

B. Device Names

Proprietary Name:	Biotest Anti-EBV Recombinant EBNA IgG
Common Name:	EBNA IgG
Classification Name:	Epstein-Barr virus serological reagents

C. Legally Marketed Device

Biotest Diagnostics claims substantial equivalence to the EBNA IgG ELISA Kit (K946158) currently in commercial distribution by INCSTAR Corporation, Stillwater, MN.

D. Device Description

Using recombinant DNA technology, Biotest has developed three highly purified EBV antigens for use in their ELISA test system.

- EBNA-1 p72: Major antigen of the EBNA complex. The recombinant protein does not contain the glycine-alanine copolymer, a structural feature of EBNA-1, which shows cross-reactivities with certain autoantibodies and CMV (IgM response).
- EA-D p64: Early antigen. Dominant immunogen of the EA-D complex.
- EA p138: Early antigen and major DNA binding protein. This highly reactive antigen is not detectable in EA immunofluorescence assays based on chemically induced Raji cells (deletion within the Raji genome).

Biotest Anti-EBV ELISA TESTS

Biotest Anti-EBV recombinant	recombinant antigens			monoclonal secondary antibody (HRP-conjugated)	
	p72	p54	p134	anti-human IgG	anti-human IgM
EA IgM		X	X		X
EA IgG		X	X	X	
EBNA IgG	X			X	

The EBV immune status will be determined by the detection of specific antibodies directed against EBV proteins according to the principle of the indirect ELISA. The antigens are purified to apparent homogeneity and immobilized on the solid phase (microtest plate, 96 wells). If the patient's serum contains specific antibodies they will bind during the first incubation. Non-specific antibodies are removed by washing steps. During a second incubation the captured IgG antibodies are labeled. This is performed by addition of murine monoclonal anti-human IgG antibody-enzyme-conjugates. The final reaction converts a colorless substrate to a colored product. The concentration of color after a definite time is related to the concentration of antibody in the serum sample.

E. Intended Use

The Biotest EBNA IgG ELISA is an enzyme immunoassay using a recombinant antigen for the qualitative detection of IgG antibodies to the Epstein-Barr Virus (EBV) EBNA-1 (Nuclear Antigen 1) in human serum or plasma. Results obtained with this test, in conjunction with other clinical and patient data obtained in assays for other Epstein-Barr antigens such as Early Antigen IgG and IgM, assist in serological diagnosis of EBV infection in pediatric and adult populations.

F. Comparison with Predicate Device

A summary comparison of the features of the Biotest EBNA IgG and the INCSTAR EBNA IgG test kits is provided in Table 1 below:

Table 1
Feature Comparison of Biotest and INCSTAR EBNA IgG Test Kits

	Biotest	INCSTAR
Intended Use	Detection of IgG antibodies to EBV EBNA-1 Qualitative only	Detection of IgG antibodies to EBV EBNA-1 Qualitative and semi-quantitative
Assay Method	ELISA	ELISA
Reactive Ingredients	Recombinant EBV (EBNA-1 p72) Peroxidase-conjugated monoclonal anti-human IgG (mouse)	EBNA-1 peptide Peroxidase - conjugated goat anti-human IgG
Specimen: Type	Serum or plasma	Serum
Min. Volume	25 μl	50 μl
Storage	2 - 8°C or -20°C	2 - 8°C/7days or -20°C
Controls	Negative Positive	Negative Low Positive High Positive
Chromogen	TMB	TMB
Results: Evaluation (spectrophotometer)	450 nm	450 nm
Kit Size	96 tests	96 tests

G. Performance Data

Sensitivity/Specificity

The performance of the Biotest EBNA IgG ELISA was evaluated in a clinical study of 408 patient samples conducted at two geographically distinct locations. Samples were obtained from both pediatric and adult patients (ages 1 to 74) representing acute (139), late acute (34), recent past (12), past (120), reactivation (22), past/probable reactivation (11), and negative (70) disease stages of EBV infection.

Two methods were used to evaluate the performance of the Biotest EBNA IgG ELISA: direct comparison with commercially available or published EBNA anti-complement immunofluorescence (ACIF) tests, and comparison with clinical interpretation (stage of infection based on antibody patterns and clinical diagnosis at the time the specimen was drawn).

Results of the direct comparison with ACIF for both sites combined demonstrated a relative sensitivity of 86.8% and a relative specificity of 97.1%.

Table 1

Clinical Site 1
Direct Comparison to ACIF

	EBNA ACIF		
	+	-	**Total**
Biotest +	95	0	95
Biotest -	24	88	112
Total	119	88	207

Relative Sensitivity = 79.8% (C.I. = 72.6 to 87%)
Relative Specificity = 100% (C.I. = 95.9 to 100%)
Relative Agreement = 88.4%

Table 2

Clinical Site 2
Direct Comparison to ACIF

EBNA ACIF			
	+	-	**Total**
Biotest +	76	6	82
Biotest -	2	116	118
Total	78	122	200

Relative Sensitivity = 97.4% (C.I. = 91 to 99.7%)
Relative Specificity = 95.1% (C.I. = 89.2 to 98.2%)
Relative Agreement = 96.0%

Table 3

Combined Site Results
Direct Comparison to ACIF

EBNA ACIF			
	+	-	**Total**
Biotest +	171	6	177
Biotest -	26	205	231
Total	197	211	408

Relative Sensitivity = 86.8% (C.I. = 82.1 to 91.5%)
Relative Specificity = 97.1% (C.I. = 93.9 to 98.9%)
Relative Agreement = 92.1%

Twenty-four (24) of the 25 Biotest EBNA IgG negative/ACIF positive samples were further tested with a commercially available EBNA-1 IgG ELISA method and an in-house validated Western Blot for EBNA-2. The results of this testing showed that all 24 samples were negative with the commercially available EBNA-1 IgG ELISA. Further, 21 of the 24 samples were positive in the Western Blot for EBNA-2 antibodies, indicating possible mixed reactions in the EBNA ACIF.

Results based on Clinical Interpretation of all patient samples where Biotest ELISA EBNA-1 antibody responses matched expected serological pattern analysis for each state of infection, including - Acute, Convalescent (Late Acute or Recent Past), Past, Reactivation and Probable Reactivation/past, and Negative.

Clinical Interpretation					
	Acute	**Convalescent**	**Past**	**Reactivation**	**Negative**
Result matches Biotest	139	44	118	32	1
Result does not match Biotest	0	2	2	1	69
Sensitivity Specificity 95% to C.I.%	100.0% N/A 97.4 - 100	95.6% N/A 85.2 - 99.5	98.3% N/A 94.1 - 99.8	96.9% N/A 84.2 - 99.9	N/A 98.6% 92.3 - 100

Total Clinical Sensitivity = 98.5% (C.I. = 96.6 to 99.5%)
Total Clinical Specificity = 98.6% (C.I. = 92.3 to 100%)
Total Clinical Agreement = 98.5%

Note: C.I. = 95% confidence intervals calculated by the exact method.

Cross Reactivity

No cross reactivity was observed when the Biotest EBNA IgG was used to test the following samples with detectable levels of IgG to:

Herpes Simplex Virus I/II (n = 27)
Varicella Zoster Virus (n = 50)
Cytomegalovirus (n = 16)

Reproducibility

To evaluate the reproducibility of the Biotest EBNA IgG ELISA, a panel of 10 patient serum specimens (low to high positive) was tested at the clinical sites. The mean, standard deviation (S.D.) and coefficient of variation (C.V.) for inter-run, intra-run and inter-lab reproducibility are presented below.

Site #1

	Inter-Run (n = 10)			Intra-Run (n = 8)		
Panel #	Mean	S.D.	% C.V.	Mean	S.D.	% C.V.
1	1.598	0.163	10.2	1.315	0.153	11.7
2	0.624	0.072	11.6	0.646	0.083	12.8
3	0.942	0.119	12.6	0.642	0.083	12.9
4	0.306	0.042	13.7	0.244	0.022	8.8
5	1.548	0.120	7.7	1.124	0.173	15.4
6	0.583	0.087	14.9	0.418	0.021	4.9
7	0.722	0.102	14.1	0.571	0.060	10.5
8	1.836	0.303	16.5	1.808	0.123	6.8
9	1.927	0.187	9.7	2.032	0.283	13.9
10	2.408	0.262	10.9	2.153	0.104	4.8

Site #2

	Inter-Run (n = 4)			Intra-Run (n = 24)		
Panel #	Mean	S.D.	% C.V.	Mean	S.D.	% C.V.
1	1.504	0.167	11.1	1.314	0.212	16.2
2	0.801	0.134	16.7	0.609	0.109	17.9
3	1.208	0.165	13.7	0.964	0.161	16.7
4	0.348	0.047	13.6	0.423	0.082	19.4
5	1.478	0.085	5.8	1.412	0.269	19.0
6	0.635	0.121	19.1	0.683	0.112	16.3
7	0.706	0.119	16.8	0.740	0.127	17.2
8	1.949	0.212	10.9	2.181	0.108	5.0
9	2.280	0.264	11.6	2.335	0.233	10.0
10	2.908	0.343	11.8	2.676	0.290	10.9

Inter-Lab (n = 14)

Panel #	Mean	S.D.	% C.V.
1	1.571	0.164	10.4
2	0.674	0.121	17.9
3	1.018	0.178	17.5
4	0.318	0.046	14.5
5	1.528	0.113	7.4
6	0.598	0.096	16.0
7	0.718	0.102	14.3
8	1.868	0.277	14.8
9	2.028	0.260	12.8
10	2.551	0.360	14.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUN 9 1999

Ms. Patricia E. Bonness
Official Correspondent
Biotest Diagnostics Corporation
66 Ford Road
Suite 131
Denville, New Jersey 07834

Re: K983841
Trade Name: Biotest Anti-EBV Recombinant EBNA IgG
Regulatory Class: I
Product Code: LSE
Dated: March 15, 1999
Received: March 31, 1999

Dear Ms. Bonness:

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.

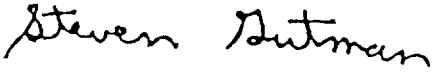
If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially 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 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 (if known): _____

Device Name: Biotest Anti-EBV Recombinant EBNA IgG

Indications For Use:

The Biotest EBNA IgG ELISA is an enzyme immunoassay for the detection of IgG antibodies to the Epstein-Barr (EBV) EBNA-1 (Nuclear Antigen-1) in human serum or plasma.

It is indicated for use, in conjunction with other clinical and patient data obtained in assays for other Epstein-Barr antigens such as Early Antigen IgG and IgM, in the serological diagnosis of EBV infection.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Woody Dubois

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K983841

Prescription Use X OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

(Optional Format 1-2-96)