

FEB 1 2000

K993724

**MRL Diagnostics
HSV-2 ELISA IgG
Catalog No. EL0920G**

**510(k) Summary of Safety and Effectiveness
Prepared January 10, 2000 (Page 1 of 6)**

Applicant MRL Diagnostics
a Focus/MRL Inc. Company
10703 Progress Way
Cypress, California 90630

**Establishment
Registration No** 2023365

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Summary Date January 10, 2000

Device Name HSV-2 ELISA IgG

Classification Herpes Simplex Virus Serological Reagents
21 CFR §866.3305
Class III

**Predicate
Device**

- 1) HSV-2 ELISA Test System, Zeus Scientific, Inc.
- 2) HSV-2 Western Blot, University of Washington
- 3) HSV-2 Culture, University of Washington

Device Description	<p>In the MRL Diagnostics HSV-2 ELISA IgG assay, the polystyrene microwells are coated with recombinant gG-2 antigen. Diluted serum samples and controls are incubated in the wells to allow specific antibody present in the samples to react with the antigen. Nonspecific reactants are removed by washing, and peroxidase-conjugated anti-human IgG is added and reacts with specific IgG. Excess conjugate is removed by washing. Enzyme substrate and chromogen are added, and the color is allowed to develop. After adding the Stop Reagent, the resultant color change is quantified by a spectrophotometric reading of optical density (OD). Sample optical density readings are compared with reference cut-off OD readings to determine results.</p>
Intended Use	<p>MRL Diagnostics' HSV-2 ELISA IgG test is intended for qualitatively detecting the presence or absence of human IgG class antibodies to HSV-2 in human sera. In conjunction with the MRL HSV-1 ELISA IgG, the test is indicated for testing sexually active adults or expectant mothers for aiding in the presumptive diagnosis of HSV infection. The predictive value of a positive or negative result depends on the population's prevalence and the pretest likelihood of HSV-2 infection. The performance of this assay has not been established for use in a pediatric population, for neonatal screening, for testing of immunocompromised patients, or for use with automated equipment.</p>

Expected Values An outside investigator assessed the device with masked, archived and unselected sera from 1) sexually active adults over the age of 14 (n = 246), and 2) from expectant mothers (n = 241). The reference method was a HSV-2 Western blot from a Pacific Northwest university. The observed prevalences and the hypothetical predictive values for the two populations are shown in the tables below. The positive predictive value will decrease proportionally to the prevalence of HSV infection as reflected in the table below. The calculations are based on MRL HSV-2 ELISA IgG having 1) a hypothetical sensitivity of 96.1% & a hypothetical specificity of 97.0% (sexually active adults), and 2) a hypothetical sensitivity of 100% and a hypothetical specificity of 96.1% (expectant mothers).

Observed Prevalence with Sexually Active Adults & Expectant Mothers

Population	HSV-2 Sero-status	Observed Prevalence	
		WB	MRL ELISA
Sexually Active Adults *	neg	68.5%	67.2%
	+	31.5%	32.4%
Expectant Mothers †	neg	75.6%	72.3%
	+	24.4%	27.3%

* Excludes 5 atypical Western blots and 1 ELISA equivocal.

† Excludes 3 atypical Western blots and 1 ELISA equivocal.

Prevalence vs. Hypothetical Predictive Values

Prevalence	Sexually Active Adults		Expectant Mothers	
	PPV	NPV	PPV	NPV
50%	97.0%	97.0%	96.2%	96.1%
40%	95.5%	98.0%	94.5%	97.4%
30%	93.2%	98.7%	91.7%	98.3%
25%	91.4%	99.0%	89.5%	98.7%
20%	88.9%	99.2%	86.5%	99.0%
15%	85.0%	99.5%	81.9%	99.3%
10%	78.1%	99.7%	74.0%	99.6%
5%	62.8%	99.8%	57.4%	99.8%

Note: Sexually active adult and expectant mother populations in different geographic areas may produce different frequency distributions from the table above. Each laboratory should establish frequency distributions for their specific patient populations.

Relative Sensitivity and Relative Specificity with Expectant Mothers An outside investigator assessed the device's relative sensitivity and relative specificity with sera from expectant mothers (n = 241). The sera were sequentially submitted to the laboratory, archived, and masked. The reference method was a HSV-2 Western blot (WB) from a Pacific Northwest university. Of 3 atypical WBs, ELISA was 1 equivocal and 2 negatives. Of 58 WB positives, ELISA was 58 positive. Of 180 WB negatives, ELISA was 172 negatives, 7 positives, and 1 equivocal.

Relative Sensitivity and Relative Specificity with Expectant Mothers (n = 241)

Characteristic	% (EL/WB)*	95% CI
Sensitivity relative to Western blot	100% (58/58)	93.8-100%
Specificity relative to Western blot	96.1% (172/179)	92.1-98.4%

* Excludes three atypical Western blots and one ELISA equivocal

Relative Sensitivity and Relative Specificity with Sexually Active Adults An outside investigator assessed the device's relative sensitivity and relative specificity with sera from sexually active adults over the age of 14 (n = 246). The sera were sequentially submitted to the laboratory, archived, and masked. The reference method was a HSV-2 Western blot from a Pacific Northwest university. Of 5 atypical WBs, ELISA was 2 equivocal, 2 negative and 1 positive. Of 76 WB positives, ELISA was 73 positive and 3 negative. Of 165 WB negatives, ELISA was 159 negative, 5 positive, and 1 equivocal.

Relative Sensitivity and Relative Specificity with Sexually Active Adults (n = 246)

Characteristic	% (EL/WB)*	95% CI
Sensitivity relative to Western blot	96.1% (73/76)	88.9-99.2%
Specificity relative to Western blot	97.0% (159/164)	93.0-99.0%

* Excludes five atypical Western blots and one ELISA equivocal

Relative Sensitivity with Culture Positives An outside investigator assessed the device's relative sensitivity using sera from culture positive patients (n = 63). Reference methods included culture (infection) and a HSV-2 Western blot (antibody) from a Pacific Northwest university. Of 5 atypical WBs, ELISA was 2 equivocal, 2 negative and 1 positive. Of 63 culture positives, ELISA was 61 positive and 2 negative, and WB was 62 positive and 1 negative. Of 62 WB positives, ELISA was 61 positive and 1 negative.

Relative Sensitivity with Culture Positives (n = 63)

Characteristic	% (EL/WB or Culture)	95% CI
Sensitivity relative to culture	96.8% (61/63)*	89.0-99.6%
Sensitivity relative to Western blot	98.4% (61/62)*	91.3-100%

*Of the 2 ELISA negatives, one was WB positive and the other WB negative.

Agreement with CDC Panel The following information is from a serum panel obtained from the CDC and tested by MRL Diagnostics. The results are presented as a means to convey further information on the performance of this assay with a masked, characterized serum panel. This does not imply an endorsement of the assay by the CDC. The panel consists of 37% positive and 63% negative samples. The MRL Diagnostics HSV-2 ELISA IgG demonstrated 100% total agreement with the CDC results. Of the results obtained by MRL Diagnostics, there was 100% agreement with the positive specimens and 100% agreement with the negative specimens.

Relative Specificity with a Low Prevalence Population An outside investigator assessed the device's relative specificity using sera from a population of college students claiming to lack sexual experience (n = 81), and having a published HSV-2 antibody prevalence of 2% (4/186).† The laboratory reference method was a HSV-2 Western blot from a Pacific Northwest university. One atypical WB was an ELISA negative. Of 78 WB negatives, ELISA was 77 negative and 1 positive. Of 2 WB negatives, ELISA was 2 positive.

Relative Specificity with a Low Prevalence Population (n = 81)

Characteristic	% (EL/WB)*	95% CI
Specificity relative to Western blot	98.7% (77/78)	93.1-100%
Sensitivity relative to Western blot	100% (2/2)	15.8-100%

* Excludes one atypical Western blot.

† Corey, L., A. Wald, *New Developments in the Biology of Genital Herpes*, in *Clinical Management of Herpes Viruses*, p.46.

Type Specificity with HSV-1 Western Blot Positives An outside investigator assessed the device's type specificity using HSV-1 Western blot positive and HSV-2 Western Blot negative sera from the above described populations (n = 287): expectant mothers, sexually active adults, low prevalence persons, and HSV-1 culture positives. Of 287 HSV-1 WB positive and HSV-2 WB negative samples, ELISA was 276 negatives, 1 equivocal and 10 positives.

Type Specificity with HSV-1 Western Blot Positives (n = 287)

Characteristic	% (EL/WB)*	95% CI
Type-specificity relative to Western blot	96.5% (276/286)	93.7-98.3%
Type cross-reactivity relative to Western blot	3.5% (10/286)	1.7-6.3%

* Excludes one equivocal ELISA result.

Cross-reactivity with Taxonomically Related Viruses MRL assessed the device's cross-reactivity using sera (n = 27) from 1) HSV sero-negative by another manufacturer's FDA cleared HSV ELISAs, and 2) IFA IgG positive for taxonomically similar viruses including CMV, EBV VCA, HHV6 and VZV. Discrepant between the FDA cleared HSV ELISAs and the MRL device were analyzed using a type specific Western blot from a major university located in the Northwestern United States.

Cross-reactivity with Taxonomically Related Viruses (n = 27)

IFA IgG Pos	% Agreement Negative*	95% CI
CMV	91.7% (11/12)	61.5-99.8%
EBV VCA	90.9% (20/22)	70.8-98.9%
HHV6	90.9% (20/22)	70.8-98.9%
VZV	90.5% (19/21)	69.6-98.8%
Total	90.9% (70/77)	82.2-96.3%

* Excludes 3 Western blot positives, and one discrepant that was not analyzed with the Western blot because of insufficient volume

Intra-assay & Inter-assay Reproducibility An internal investigator assessed the device's intra-assay and inter-assay reproducibility by assaying seven samples in duplicate, twice a day, for twenty days, for a total of forty runs. Two sets of samples were masked duplicates.

Inter-lot Reproducibility An internal investigator assessed the device's inter-lot reproducibility. Five samples were run on three separate days with three separate lots. For one lot, the samples were run in triplicate, and run in duplicate with the other two lots. Each of the three lots had a different lot of Antigen Wells.

Inter-laboratory Reproducibility An internal investigator and two off-site laboratories assessed the device's inter-laboratory reproducibility. Each of the three laboratories ran seven samples in triplicate on three different days. Three points were excluded because an incorrect sample (instead of sample 27) was run one day.

Reproducibility

Sample	Inter- & Intra-assay			Inter-lot		Inter-Laboratory		
	Index Mean	Intra-assay %CV	Inter-assay %CV	Index Mean	Index %CV	Index Mean	%CV of Lab Means	Mean of Lab %CVs
21*	0.18	20.5%	15.9%	0.28	52.4%	0.23	19.6%	17.3%
26*	0.18	12.2%	12.4%	NA	NA	0.26	33.1%	20.7%
22**	1.23	6.3%	6.2%	1.16	5.1%	1.19	3.9%	7.8%
27**	1.22	5.2%	6.3%	NA	NA	1.14	14.1%	8.8%
23	1.79	4.7%	5.5%	1.76	5.4%	1.73	5.2%	7.1%
24	3.42	3.2%	7.9%	3.18	16.7%	2.77	11.0%	10.8%
25	8.17	3.0%	6.9%	7.99	7.4%	6.82	18.6%	4.5%

* #21 & #26 are same material. ** #22 & #27 are same material.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

FEB 1 2000

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Re: K993724
Trade Name: HSV-2 ELISA IgG
Regulatory Class: III
Product Code: MYF
Dated: January 10, 2000
Received: January 13, 2000

Dear Mr. Wagner:

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 (Pre-market 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.

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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" (21CFR 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 (301) 443-6597 or at its internet address "<http://www.fda.gov/cdrh/dsma/dsmamain.html>".

Sincerely yours,

A handwritten signature in black ink that reads "Steven Gutman". The signature is written in a cursive, slightly slanted style.

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): K993724

Device Name: HSV-2 ELISA IgG

Indications for Use: MRL Diagnostics' HSV-2 ELISA IgG test is intended for qualitatively detecting the presence or absence of human IgG class antibodies to HSV-2 in human sera. In conjunction with the MRL HSV-1 ELISA IgG, the test is indicated for testing sexually active adults or expectant mothers for aiding in the presumptive diagnosis of HSV infection. The predictive value of a positive or negative result depends on the population's prevalence and the pretest likelihood of HSV-2 infection. The performance of this assay has not been established for use in a pediatric population, for neonatal screening, for testing of immunocompromised patients, or for use with automated equipment.

LDI International
BTM01-033 M

(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 K993724

PRESCRIPTION USE X

(Optional Format 3-10-98)