

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number: K071510

B. Purpose for Submission: Initial Premarket Notification

C. Measurand: Human IgG class antibodies to herpes simplex virus type 2 (HSV-2)

D. Type of Test: Qualitative Immunochromatographic Assay- utilizes nitrocellulose membrane lateral flow

E. Applicant: Focus Diagnostics, Inc.

F. Proprietary and Established Names: HerpeSelect® Express IgG

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
MYF [Enzyme linked immunosorbent assay, herpes simplex virus, HSV-2]	Class II	HSV serology device 21 CFR 866.3305	Microbiology (83)

H. Intended Use:

HerpeSelect® Express is a rapid test intended for qualitatively detecting the presence or absence of human IgG class antibodies to herpes simplex virus type 2 (HSV-2) in human whole blood (venous or capillary) or serum. The test is indicated for testing sexually active adults or pregnant women to aid in the presumptive diagnosis of HSV-2 infection.

The HerpeSelect® Express IgG device has not been established for use in the pediatrics population, for neonatal screening, or for testing immunocompromised patients. This kit is not intended for self-testing, and this test is neither FDA cleared nor approved for testing blood or plasma donors.

3) Special conditions for use statement(s): Prescription use only

4) Special instrument requirements: No special instruments are required for the device

I. Device Description: The HerpeSelect® Express IgG is a rapid one step qualitative test for detection of human IgG class antibodies to herpes simplex virus type 2 (HSV-2) in human whole blood (venous or capillary) or serum samples based on lateral flow immunochromatographic assay. The test is indicated for testing sexually active adults or

pregnant women for aiding in the presumptive diagnosis of HSV infection. It is a Class II noninvasive device individually packaged in a foil pouch. The device contains three separate active components (purified native HSV-2 antigen, recombinant HSV-1 antigen, and anti-human IgG antibody) bound onto a nitrocellulose membrane, a buffer pad and conjugate pad enclosed in a plastic housing. The conjugate pad carrying dried antibody-gold conjugate specific for human IgG is located between the sample well and buffer pad. The HSV-2 antigen is the test line and anti-human IgG antibody is a control line. HSV-2 positive result in the sample is indicated by the formation of pink lines in both test and control regions. Pink line formation only in control region verifies the device functionality, not an indication of HSV-2 positive results. Recombinant HSV-1 antigen pre-absorbs the HSV-1 antibodies from the sample and is hidden in the device; therefore, HSV-1 line formation is not visible in the test.

During testing, whole blood (venous or capillary) or serum is applied into the sample application well and filtered through the blood separation membrane and absorbed into the test strip; the test housing lid is opened; buffer is applied in the buffer port to cause the antibody-gold conjugate specific for human IgG and sample to migrate via capillary action through the nitrocellulose membrane into the result region of the device and generates a chromogenic reaction (pink line) in the presence of HSV-2.

J. Substantial Equivalence Information:

a) Predicate device name (s):

The HerpeSelect[®] 1 and 2 immunoblot

Reference Method for clinical evaluation: HerpeSelect[®] 1 and 2 immunoblot

b) Predicate K numbers (s):

K000238

Comparison with predicate: Two devices were listed as predicate devices. The HerpeSelect2 Immunoblot IgG was the typing reference method for clinical data evaluation and calculation of sensitivity and specificity.

Note: It is important to compare the device detecting HSV-2 to a well characterized western blot or a FDA cleared immunoblot for the purpose of clinical data evaluation.

Item	Device	Predicate
Name	HerpeSelect® Express IgG	HerpeSelect 1 and 2 Immunoblot IgG
Similarity between Device and Predicates		
Intended use	Focus Diagnostics' HerpeSelect® Express is a rapid test intended for qualitatively detecting the presence or absence of human IgG class antibodies to herpes simplex virus type 2 (HSV-2) in human whole blood (venous or capillary) or serum. The test is indicated for testing sexually active adults or pregnant women to aid in the presumptive diagnosis of HSV-2 infection. The predictive value of a positive or negative result depends on the population's prevalence and the pre-test likelihood of HSV-2 infection. This kit is not intended for self-testing, and is not approved for testing blood donors or plasma donors.	Focus Diagnostics' HerpeSelect® 1 and 2 Immunoblot IgG test is intended for qualitatively detecting the presence or absence of human IgG class antibodies to HSV-1 and HSV-2 in human sera. The test is indicated for testing sexually active adults or pregnant women for aiding in the presumptive diagnosis of HSV-1 and HSV-2 infection. The predictive value of a positive or negative result depends on the population's prevalence and the pretest likelihood of HSV-1 and HSV-2 infection. The performance of this assay has not been established for use in a pediatric population, for neonatal screening, for testing of immuno-compromised patients, for use by a point of care facility or for use with automated equipment.
Indications for use	The test is indicated for testing sexually active adults or pregnant women for aiding in the presumptive diagnosis of HSV-2 infection.	The test is indicated for testing sexually active adults or pregnant women for aiding in the presumptive diagnosis of HSV-1 and HSV-2 infection.
Immunoglobulin Type	IgG	IgG
Sample matrix	Human whole blood (venous or capillary) or Serum	Serum
Difference between Device and Predicate		
Antigen	HSV-1: Recombinant gG1 (pre-absorption line) HSV-2: Native gG2	HSV-1: Recombinant gG1 HSV-2: Recombinant gG2 antigen
Strain	HSV-1: N/A (recombinant antigen) HSV-2: Lovelace	HSV-1: N/A (recombinant antigen) HSV-2: N/A (recombinant antigen)
Host Cell Line	HSV-1: Baculovirus HSV-2: Vero	HSV-1: Baculovirus HSV-2: Baculovirus
Methodology	Nitrocellulose Membrane Lateral Flow	Immunoblot assay
CLIA complexity	Moderate	Moderate

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

1. Guidance for Industry and FDA Staff, Format for Traditional and Abbreviated 510(k), 08/12/2005

2. Guidance for Industry and Food and Drug Administration Staff; Class II Special Controls Guidance Document: Herpes Simplex Virus Types 1 and 2 Serological Assays 04/09/2007

L. Test Principle:

The HerpeSelect® Express is a qualitative immunochromatographic assay in a plastic cartridge that contains three separate active components (purified native HSV-2 antigen, recombinant HSV-1 antigen, and anti-human IgG antibody) bound onto a nitrocellulose membrane, a buffer pad and conjugate pad enclosed in a plastic housing. The conjugate pad carrying dried antibody-gold conjugate specific for human IgG is located between the sample application well and buffer pad. Sample is applied to the sample well and is allowed to filter through the nitrocellulose membrane for 30 sec. The buffer is applied in the buffer port to cause the antibody-gold conjugate specific for human IgG and sample to migrate via capillary action through the nitrocellulose membrane into the result region of the device and generates a chromogenic reaction (pink line) in the presence of HSV-2. Positive test is indicated by formation of pink line in the test zone (for HSV-2 IgG present in the sample) and control zone (human IgG present in the sample). In case of negative sample, no pink line is seen in test zone while formation of pink line in control zone will indicate the functionality of the device.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:* A reproducibility study was conducted at three external US laboratories i.e. Rocky Mountain Region of the United States; a student health clinic in the Southeastern United States, and an Sexual Transmitted Disease (STD) clinic located in the Pacific Northwest. Reactivity for the reproducibility samples was determined using ELISA index range. Based on the ELISA Index (shown in the following table, column 1), a coded panel of 10 samples was prepared to represent low to mid positive analyte levels and was tested at all three sites on three days by three operators. The Inter/Intra-operator and Inter/Intra-site reproducibility results are summarized in the following tables.

ELISA Range	Sample ID	Inter-Lot Reproducibility		Inter-Operator			Inter-Site		
		Mean	%CV	Accuracy	Precision	%CV	Accuracy	Precision	%CV
High Negative (0.70-0.90)	HSV-1	100.0%	0.0%	100.0%	100.0%	0.0%	100.0%	100.0%	0.0%
Borderline (1.10-3.50)	HSV-2	100.0%	0.0%	98.8%	100.0%	3.7%	98.8%	97.8%	2.2%
Negative (<0.90)	HSV-11	100.0%	0.0%	98.1%	99.9%	5.7%	98.1%	96.7%	3.3%
High Positive (>3.5)	HSV-12	100.0%	0.0%	100.0%	100.0%	0.0%	100.0%	100.0%	0.0%
Positive (1.10-3.50)	HSV-13	100.0%	0.0%	97.5%	99.9%	7.6%	97.5%	95.6%	4.4%
Low Positive (0.90-1.10)	HSV-14	100.0%	0.0%	59.9%	99.4%	64.6%	59.9%	67.2%	32.8%
Negative (<0.90)	HSV-15	77.8%	24.7%	84.0%	99.7%	28.2%	84.0%	81.6%	18.4%
Positive (1.10-	HSV-26	100.0%	0.0%	98.8%	100.0%	3.7%	98.8%	97.8%	2.2%

3.50)									
Negative (0.90)	HSV-27	100.0%	0.0%	100.0%	100.0%	0.0%	100.0%	100.0%	0.0%
Positive	HSV-28	100.0%	0.0%	98.8%	100.0%	3.7%	98.8%	97.8%	2.2%
Intra-Operator									
Operator	Accuracy			Precision			%CV		
1	96.7%			81.1%			18.9%		
2	98.9%			93.8%			6.2%		
3	90.0%			66.1%			33.9%		
4	98.9%			93.8%			6.2%		
5	87.8%			64.8%			35.2%		
6	96.7%			81.1%			18.9%		
7	90.0%			78.5%			21.5%		
8	92.2%			75.5%			24.5%		
9	91.1%			69.7%			30.3%		
Intra-Site									
Site	Accuracy			Precision			%CV		
1	95.2%			78.0%			22.0%		
2	94.4%			77.4%			22.6%		
3	91.1%			74.5%			25.5%		

b. *Linearity/assay reportable range:* NA

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):* NA

d. *Detection limit:* This device is for the HSV-2 antibody detection and was not tested for the limit of detection. There is no standard available for measuring the HSV antibody units in the serum.

e. *Analytical specificity:*

1. **Cross Reactivity:** The cross-reactivity studies for the HerpeSelect® Express were designed to evaluate potential cross reactivity from immunoglobulins (IgG) directed against closely-related members of the herpes virus family that may clinically confused with herpes simplex (e.g. HSV-1, VZV, CMV, EBV, rubella virus) and from other conditions that may result from atypical immune system activity (e. g. rheumatoid factor (RF), anti-nuclear antibodies (ANA). A total of 213 sero-positive samples for one of the closely related members (HSV-1, VZV, CMV, EBV, rubella virus, RF, ANA) were shown negative by testing with the HerpeSelect2 ELISA IgG predicate device. These samples were further tested with the HerpeSelect2 Express IgG. Test results from the HerpeSelect2 Express IgG showed only 4.2% (9/213) of combined cross reactivity with these samples.

Express Agreement Cross-Reactant

Cross-reactant	n	HerpeSelect Express			% Cross-Reactivity
		Positive	Negative	Invalid	
HSV-1 IgG +	25	0	25	0	0.0% (0/25) 95%CI 0.0 - 13.7%
Rubella +	25	1	24	0	4.0% (1/25) 95%CI 0.0 – 20.4%
VZV IgG +	42	4	38	0	9.5% (4/42) 95%CI 2.7 – 22.6%
EBV IgG +	25	1	24	0	4.0% (1/25) 95%CI 0.0 – 20.4% %
CMV IgG +	32	1	31	0	3.1% (1/32) 95%CI 0.0-16.2%
RF +	33	1	32	0	3.0% (1/33) 95%CI 0.0 – 15.8%
ANA +	31	1	30	0	3.2% (1/31) 95%CI 0.0-15.8%
Combined Cross-reactants	213	9	204	0	4.2% (9/213) 95%CI 1.9-7.8%

2. Interference: The device performance was evaluated with the presence of interferents. Sera from two subjects were selected by HerpeSelect ELISA IgG for the interference studies:

- i) One serum positive for herpes simplex virus-2 and negative for herpes simplex virus-1.
- ii) One serum negative for both herpes simplex virus 1 and herpes simplex virus 2.

These serum samples were divided in two aliquots. One aliquot was used to establish baseline levels for triglycerides, albumin, bilirubin, and hemoglobin for each subject. The commercially available interferents were used to spike the other aliquot at the level (e.g. triglycerides 10 mg/ml, albumin 60 mg/ml, bilirubin 0.2 mg/mL, hemoglobin 220 mg/mL) which exceeded the expected human range. The spiked samples were tested again in the assay to determine if the elevated levels of interferents affected the assay. There was no effect of the interferents on the performance of this assay.

f. *Assay cut-off:* NA

2. Comparison studies:

a. *Method comparison with reference method:*

The HerpeSelect® 1 and 2 immunoblot

b. *Matrix comparison: Serum, Blood (Venous and Capillary)*

Since the *HerpeSelect® Express IgG* intended use lists venous blood collected in the EDTA treated tubes as well as capillary blood as an additional specimen type, analytical matrix equivalence studies were conducted to demonstrate the equivalence between serum and blood matrices. Negative serum and negative whole blood matrices were spiked with *HerpeSelect®2 ELISA IgG* positive serum. The two spiked samples were serially diluted (1:2, 1:4, 1:8, 1:16) with

the same negative matrix i.e. spiked negative serum with negative serum matrix and spiked whole blood with negative whole blood. Negative and positive controls used for the matrices comparison studies were negative matrices without spiking and undiluted spiked samples. Each sample was tested in triplicate. Three of three whole blood replicates showed end-point at 1:4 whereas two of three of the serum replicates were at 1:8 and one at 1:4. The difference between serum and whole blood matrices was insignificant.

3. Clinical studies:

a. *Clinical Sensitivity:* NA

b. *Clinical specificity:* NA

c. Other clinical supportive data (when a. and b. are not applicable):

Performance Characteristics

The Focus Diagnostics tested a total of 1089 samples derived from: 1) Pregnant women (n= 401); 2) Sexually active adults (n=575); and 3) Non-sexually active adults (low prevalence population, n= 104). The testing for the pregnant women and sexually active adults was performed at three sites whereas testing for the non-sexually active populations was conducted at two sites only. Three different sample matrices i.e. a) serum, b) venous blood, and c) capillary blood from each individual was tested with *HerpeSelect® Express IgG* and compared with a reference method predicate device - *HerpeSelect® Immunoblot 1 and 2 IgG* for sensitivity and specificity.

1. Pregnant Women

a. Agreement with Pregnant Women in sera (n = 401)

Site	Immunoblot	n ¹	Express			Sensitivity	Specificity
			Positive	Negative	Invalid		
Combined Sites	Positive	117	108	6	3	92.3% (108/117) 95%CI 85.9-96.4%	N/A
Combined Sites	Negative	282	9	271	2	N/A	96.1% (271/282) 95%CI 93.1-98.0%
Combined Sites	Equivocal	0	0	0	0	N/A	N/A

b. Agreement with Pregnant Women in venous whole blood (n = 401)

Site	Immunoblot	n ¹	Express			Sensitivity	Specificity
			Positive	Negative	Invalid		
Combined Sites	Positive	117	109	8	0	93.2% (109/117) 95%CI 87.0-97.0%	N/A
Combined Sites	Negative	282	8	274	0	N/A	97.2% (274/282) 95%CI 94.5-98.8%
Combined Sites	Equivocal	0	0	0	0	N/A	N/A

¹ Two samples were not tested.

c. Agreement with Pregnant Women in capillary whole blood (n = 401)

Site	Immunoblot	n ¹	Express			Sensitivity	Specificity
			Positive	Negative	Invalid		
Combined Sites	Positive	117	111	6	0	94.9% (111/117) 95% CI 89.2-98.1%	N/A
Combined Sites	Negative	282	12	269	1	N/A	95.4% (269/282) 95% CI 92.2-97.5%
Combined Sites	Equivocal	0	0	0	0	N/A	N/A

Two samples were not tested in Immunoblot.

2. Sexually Active Adults

a. Agreement with Sexually Active Adults in sera (n = 575)

Site	Immunoblot	n ¹	Express			Sensitivity	Specificity
			Positive	Negative	Invalid		
Combined Sites	Positive	226	210	14	2	92.9% (210/226) 95% CI 88.8-95.9%	N/A
Combined Sites	Negative	343	28	315	0	N/A	91.8% (315/343) 95% CI 88.4-94.5%
Combined Sites	Equivocal	1	0	1	0	N/A	N/A

b. Agreement with Sexually Active Adults in venous whole blood (n = 575)

Site	Immunoblot	n ¹	Express			Sensitivity	Specificity
			Positive	Negative	Invalid		
Combined Sites	Positive	226	211	15	0	93.4% (211/226) 95% CI 89.3-96.2%	N/A
Combined Sites	Negative	343	26	317	0	N/A	92.4% (317/343) 95% CI 89.1-95.0%
Combined Sites	Equivocal	1	0	1	0	N/A	N/A

c. Agreement with Sexually Active Adults in capillary whole blood (n = 575)

Site	Immunoblot	n ¹	Express			Sensitivity	Specificity
			Positive	Negative	Invalid		
Combined Sites	Positive	226	212	14	0	93.8% (212/226) 95% CI 89.8-96.6%	N/A
Combined Sites	Negative	343	28	315	0	N/A	91.8% (315/343) 95% CI 88.4-94.5%
Combined Sites	Equivocal	1	0	1	0	N/A	N/A

Five samples were not tested.

3. Non-Sexually Active Individuals

a. Agreement with Non-Sexually Active Individuals in sera (n =104)

Site	Immunoblot	n ¹	Express			Sensitivity	Specificity
			Positive	Negative	Invalid		
Combined Sites	Positive	2	0	2	0	0% (0/2)	N/A
Combined Sites	Negative	101	0	101	0	N/A	100% (101/101) 95% CI 96.4-100
Combined Sites	Equivocal	0	0	0	0	N/A	N/A

b. Agreement with Non-Sexually Active Individuals in venous whole blood (n =104)

Site	Immunoblot	n	Express			Sensitivity	Specificity
			Positive				
Combined Sites	Positive	2	0	2	0	0% (0/2)	N/A
Combined Sites	Negative	101	0	101	0	N/A	100% (101/101) 95% CI 96.4-100
Combined Sites	Equivocal	0	0	0	0	N/A	N/A

c. Agreement with Non-Sexually Active Individuals in Capillary whole blood (n = 104)

Site	Immunoblot	n	Express			Sensitivity	Specificity
			Positive	Negative	Invalid		
Combined Sites	Positive	2	0	2	0	0% (0/2)	N/A
Combined Sites	Negative	101	0	101	0	N/A	100% (101/101) 95% CI 96.4-100
Combined Sites	Equivocal	0	0	0	0	N/A	N/A

One sample was not tested.

4. CDC Panel: Focus Diagnostics tested 100 samples from CDC panel that includes 65 negative and 35 positive specimens. The CDC panel samples tested with the HerpeSelect2 Express IgG showed 100% of positive (35/35) and 98.5% of negative agreement (64/65) with the CDC results.

Agreement with CDC Panel (n = 100)

CDC Result	n	HerpeSelect [®] Express Results			
		Pos	Neg	Invalid	% Agreement
Negative	65	1	64	0	98.5% (64/65) 95% CI 91.7 - 100.0%
Positive	35	35	0	0	100% (35/35) 95% CI 90.0-100.0%

4. Clinical cut-off: NA

5. Expected values/Reference range:

As described earlier, the device was assessed and compared with the predicates for masked, prospectively samples from two populations i.e. (pregnant women, n=410 and sexually active adults, n=575) and non-sexually active adults (low prevalent populations, n=104) and. The observed prevalence and the hypothetical predictive values were determined for high prevalent populations (pregnant women and sexually active adults). Results for all three matrices from negative and positive samples were shown very close agreement with the reference predicate device HerpeSelect 2 Immunoblot IgG and other predicate device HerpeSelect 2 ELISA IgG.

Observed Rate of Positives in Indicated Populations

Observed Prevalence	Observed Rate of Positives in Indicated Populations			
	HerpeSelect Express In Sera	HerpeSelect Express In Venous Whole Blood	HerpeSelect Express In Capillary Whole Blood	HerpeSelect Immunoblot
HSV-2 positives(+) with Pregnant Women	(118/400) 29.5%	(118/400) 29.5%	(124/400) 31.0%	(117/399) 29.3%
HSV-2 positives(+) with Sexually Active Adults	(241/573) 42.1%	(240/573) 41.9%	(243/573) 42.4%	(226/570) 39.6%

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion: The submitted information in this premarket notification is complete and supports a substantial equivalence decision.