August 23, 2018

Biokit, S.A.
Joan Guixe
QA & RA Director
Can Male, S/N
Llica d'Amunt, 08186
Barcelona, Spain

Re: K181334
Trade/Device Name: ADVIA Centaur Herpes-2 IgG
Regulation Number: 21 CFR 866.3305
Regulation Name: Herpes simplex virus serological assays
Regulatory Class: Class II
Product Code: MYF
Dated: May 17, 2018
Received: May 25, 2018

Dear Joan Guixe:

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. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. 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. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to 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 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Steven R. Gitterman -S for

Uwe Scherf, Ph.D.
Director
Division of Microbiology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
k183334

Device Name
ADVIA Centaur Herpes-2 IgG

Indications for Use *(Describe)*
The ADVIA Centaur® Herpes-2 IgG (HSV2) assay is for in vitro diagnostic use in the qualitative determination of IgG antibodies to herpes simplex virus type 2 (HSV-2) in human serum and plasma (EDTA and lithium heparin) using the ADVIA Centaur systems. 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 prevalence of HSV-2 infection in the population and the pre-test likelihood of HSV-2 infection.

The test is not FDA cleared for screening blood or plasma donors. The performance of this assay has not been established for immunocompromised patients, pediatric patients or matrices other than human serum and plasma (EDTA and lithium heparin).

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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Biokit
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510(K) SUMMARY

This 510(k) Summary is being submitted in accordance with the requirements of the Safe Medical Device Act of 1990 and 21 CFR 807.92.

1. Submitter's Information	Biokit, S.A. Can Malé S/N Lliçà d'Amunt 08186 Barcelona (Spain)

2. Contact Person	Joan Guixer, QA & RA Director Phone: +34 93 860 90 00 / +34 657 88 33 47 Email: jguixer@biokit.com

3. Preparation Date	May 17th , 2018

4. Device Trade Name	ADVIA Centaur Herpes-2 IgG

5. Regulatory Information	Regulation Number	21 CFR 866.3305
	Regulation Description	Herpes simplex virus serological assays
	Classification	Class II Special Controls
	Product Code	MYF
	Classification Panel	Microbiology

6. Predicate Device	K000238 (Focus HerpeSelect 1 and 2 Immunoblot IgG)

7. Indications for Use / Intended Use	The ADVIA Centaur® Herpes-2 IgG (HSV2) assay is for in vitro diagnostic use in the qualitative determination of IgG antibodies to herpes simplex virus type 2 (HSV-2) in human serum and plasma (EDTA and lithium heparin) using the ADVIA Centaur systems. 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 prevalence of HSV-2 infection in the population and the pre-test likelihood of HSV-2 infection. The test is not FDA cleared for screening blood or plasma donors. The performance of this assay has not been established for immunocompromised patients, pediatric patients or matrices other than human serum and plasma (EDTA and lithium heparin).

8. Device Description	The ADVIA Centaur Herpes-2 IgG (HSV2) assay is a fully automated two-step sandwich immunoassay using indirect chemiluminometric technology. The specimen is incubated with the Solid Phase, which contains HSV-2-specific recombinant-gG2 antigen. Antigen-antibody complexes will form if anti-HSV-2 antibody is present in the specimen. The Lite Reagent contains monoclonal anti-human IgG labeled with acridinium ester, and is used to detect HSV-2 IgG in the specimen.

COMPARISON PREDICATE		
Item	**Predicate**	**New Device**
Trade Names	Focus HerpeSelect 1 and 2 Immunoblot IgG	ADVIA Centaur Herpes-2 IgG
510K nº	K000238	K183334

Manufacturer	Focus Diagnostics Cypress, CA 90630 -USA	Siemens Heathcare Diagnostics Inc. 511 Benedict Avenue, Tarrytown, NY 10591- USA
Similarities		
Intended use	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 expectant mothers 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 immunocompromised patients, for use by a point of care facility or for use with automated equipment	The ADVIA Centaur® Herpes-2 IgG (HSV2) assay is for in vitro diagnostic use in the qualitative determination of IgG antibodies to herpes simplex virus type 2 (HSV-2) in human serum and plasma (EDTA and lithium heparin) using the ADVIA Centaur systems. 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 prevalence of HSV-2 infection in the population and the pre-test likelihood of HSV-2 infection. The test is not FDA cleared for screening blood or plasma donors. The performance of this assay has not been established for immunocompromised patients, pediatric patients or matrices other than human serum and plasma (EDTA and lithium heparin).
Measurand	To detect the presence or absence of human IgG class antibodies to HSV-1 and HSV-2	To detect IgG antibodies to herpes simplex virus type 2 (HSV-2).
Regulation Section	21 CFR 866.3305	Same

Product Code	LGC	MYF
Classification	Class II Special Controls	Same
Assay Type	Qualitative	Same
Differences		
Technology	Nitrocellulose immunoblot	Chemiluminescent immunoassay
Sample type	Human serum	Human serum and plasma (EDTA and lithium heparin)

9. Performance Summary

Precision

A precision study was performed according to CLSI EP05-A3 , using the Negative and Positive Controls as well as 6 samples prepared at different levels in the assay range. Each material was tested in duplicate, twice a day for 20 days, for a total of 80 replicates per level.

The ADVIA Centaur HSV2 assay is designed to have the following repeatability and within-lab precision requirements:

ADVIA Centaur HSV2 Level (Index)	Design Requirement	
	Repeatability % CV	Within-Lab % CV
< 0.5	NA[a]	NA
0.51–0.79	≤ 10.0%	≤ 15.0%
0.80–1.20	≤ 6.0%	≤ 8.0%
1.21–3.00	≤ 5.0%	≤ 8.0%
3.01–6.00	≤ 5.0%	≤ 7.0%
> 6.00	≤ 5.0%	≤ 7.0%

[a] NA = not applicable

The results for this study are presented below.

Precision results for the HSV-2 Assay

Specimen Type	N	Mean (Index)	Repeatability		Within-Lab	
			SD	CV (%)	SD	CV (%)
Negative Control (Plasma)	80	0.29	0.01	NA[a]	0.02	NA[a]
Positive Control (Plasma)	80	3.09	0.07	2.3	0.20	6.5
Serum 1	80	0.36	0.01	NA[a]	0.02	NA[a]
Plasma 2	80	0.63	0.02	2.4	0.04	5.9
Serum 3	80	1.08	0.05	4.3	0.08	7.2
Serum 4	80	2.58	0.09	3.6	0.20	7.6
Serum 5	80	5.29	0.09	1.7	0.34	6.4
Serum 6	80	7.62	0.17	2.2	0.47	6.1

NA[a]= Not applicable

Sample matrix

This study was performed on one ADVIA Centaur XP instrument, using 68 sets of matched samples of different matrixes (serum, serum separator tube (SST), EDTA plasma and lithium heparin plasma) from commercial sources.

The samples were analyzed in duplicate in randomized order using one reagent lot.

- Comparing Serum Separator Tube (y) vs Serum (x): (Deming regression) y = 0.00 + 0.99x, r=0.999, sample range for both matrixes 0.02-9.59 Index Value and 0.02-9.49 Index Value respectively. Note – correlation coefficient is calculated using linear regression.
- Comparing EDTA Plasma(y) vs Serum (x): (Deming regression) y= 0.00 + 0.98 x, r=0.998, sample range for both matrixes 0.02-9.59 Index Value and 0.02-9.34 Index Value respectively. Note – correlation coefficient is calculated using linear regression.
- Comparing Lithium Heparin Plasma(y) vs Serum (x): (Deming regression) y= -0.01 + 0.98 x, r=0.997, sample range for both matrixes 0.02-9.59 Index Value and 0.01-9.23 Index Value respectively. Note – correlation coefficient is calculated using linear regression.

The results supports that Serum Separator Tube is equivalent matrix to Serum, EDTA Plasma is equivalent matrix to Serum and Lithium Heparin Plasma is an equivalent matrix to Serum.

Panels

The commercial sample panels ToRCH-mixed Zeptometrix and CDC panel were analysed.

The ToRCH-mixed Zeptometrix panel included 24 characterized HSV samples. All of the samples were evaluated with the ADVIA Centaur Herpes-2 IgG assay on ADVIA Centaur XP instrument and 100% total agreement was observed with reference assay 1.

The CDC panel included 100 blind characterized HSV samples. All of the samples were evaluated with the ADVIA Centaur Herpe-2 IgG assay on ADVIA Centaur XP instrument and 100% total agreement was observed in concordance with the results provided by the CDC.

Interferences

Potential interference in the ADVIA Centaur HSV2 assay from the compounds listed below is designed to be ≤ 10%. Interfering substances at the levels indicated were tested as described in CLSI Document EP7-A2. The testing was done in three levels of samples in the assay range (high negative, low positive and positive samples) with at least one reagent lot on ADVIA Centaur XP instrument.

Testing confirmed no interference (Demonstrate ≤ 10% change in results) for the ADVIA Centaur Herpes-2 IgG up to the following concentrations:

Serum specimens that are…	Demonstrate ≤10% change in results up to…
Biotin	3500 ng/mL
Hemoglobin	500 mg/dL
Bilirubin complex	40 mg/dL
Bilirubin free	40 mg/dL
Hypoproteinemia	3 g/dL
Hyperproteinemia	12 g/dL
Lipemia	1000 mg/dL
Cholesterol	400 mg/dL

Cross-reactivity

The ADVIA Centaur HSV2 assay was evaluated for potential cross-reactivity other viral antibodies, disease-state specimens, and other populations. The HSV-2 IgG status of each specimen was verified using the Comparative Assay. Repeat equivocal specimens on the Comparative Assay were sent to a reference laboratory for Western Blot testing. Total

percent agreement for the following clinical categories was 96.9% (506/522). The following results were obtained:

Cross Reactivity Study Performance Results

Clinical Category	Number tested	ADVIA Centaur HSV2	Reference Method
		Reactive	Positive
Antibody to hepatitis B surface antigen (Anti-HBs)	10	5	6
Anti-gliadin	10	1	1
Anti-nuclear antibodies (ANA)	10	0	1
Candida albicans	10	3	3
Chlamydia trachomatis	10	4	4
Cytomegalovirus (CMV; HHV-5)	25	9	11
Elevated IgG levels	10	8	8
Elevated IgM levels	10	3	3
Epstein-Barr Virus (EBV IgG)	10	3	3
Escherichia coli	10	5	5
Flu vaccine	10	1	1
Gardenerella vaginalis	10	5	5
Hepatitis B surface antigen (HBsAg)	10	4	4
Hepatitis C Virus (HCV)	10	7	7
Herpes simplex virus type 1 (HSV-1)	117	29	31
Heterophile antibodies (EBV)	10	0	0
Human Anti-mouse antibodies (HAMA)	10	4	4
Human herpes virus 6 (HHV-6)	10	2	3
Human herpes virus 8 (HHV-8)	10	5	5
Human immunodeficiency virus (HIV)	10	9	9
Human Papillomavirus (HPV)	25	3	5

Clinical Category	Number tested	ADVIA Centaur HSV2	Reference Method
		Reactive	Positive
Multiple myeloma	10	3	3
Neisseria gonorrhoeae	10	4	4
Parvovirus B19	10	0	0
Rheumatoid factor (RF)	10	5	5
Rubella IgG	10	2	2
Syphilis	10	7	7
Systemic lupus erythematosus (SLE)	10	1	0
Toxoplasma IgG	95	26	30
Varicella Zoster virus (HHV-3)	10	1	1
Total Samples	**522**	**159**	**171**

Multisite reproducibility

Reproducibility was evaluated according to the CLSI protocol EP5-A3.25. The ADVIA Centaur HSV2 assay is designed to have reproducibility precision requirements of ≤ 15% for specimens with ≥ 0.80 Index.

A reproducibility study was conducted using 1 reagent lot at 3 external sites on the ADVIA Centaur XP instrument, using a sample panel blinded and randomized that was composed by the Controls (Negative and Positive) and 6 samples prepared at different levels in the assay range.

The protocol was run over 5 days, 2 runs per day, and 3 replicates per run for the sample pools, and for the negative and positive control materials. The data in the following table represents pooled results from the 3 sites.

The results are presented in the table below.

Multisite Precision Study Repeatability

Specimen type	N	Mean (Index)	Repeatability		Between-Run		Between-Day		Between-Site		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Negative control	90	0.31	0.01	4.5%	0.00	1.1%	0.01	1.8%	0.02	6.2%	0.02	7.9%

Specimen type	N	Mean (Index)	Repeatability		Between-Run		Between-Day		Between-Site		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Positive control	90	3.27	0.06	1.9%	0.04	1.2%	0.04	1.4%	0.06	1.8%	0.10	3.2%
Serum 1	90	0.36	0.01	2.3%	0.01	3.6%	0.01	3.1%	0.02	4.8%	0.03	7.1%
Plasma 2	90	0.64	0.01	1.8%	0.01	1.1%	0.02	2.7%	0.00	0.0%	0.02	3.4%
Serum 3	90	1.07	0.02	1.8%	0.03	2.8%	0.03	2.9%	0.03	2.8%	0.06	5.2%
Serum 4	90	2.47	0.08	3.1%	0.06	2.5%	0.05	1.8%	0.13	5.4%	0.17	7.0%
Serum 5	90	5.24	0.34	6.4%	0.12	2.3%	0.11	2.2%	0.21	4.0%	0.43	8.2%
Serum 6	90	7.87	0.14	1.8%	0.18	2.2%	0.20	2.5%	0.20	2.5%	0.36	4.6%

Clinical study

A multicenter clinical study to compare the reference device with ADVIA Centaur Herpes-2 IgG was performed. Sensitivity and specificity were determined by comparing the performance of the ADVIA Centaur HSV2 assay to a commercially available anti-HSV-2 IgG immunoblot method (Comparative Assay) and a validated Western Blot reference confirmatory test (University of Washington, Seattle). A total of 864 specimens (≥ 18 years of age), including specimens from 274 pregnant women, were collected within the United States and tested at 3 independent external laboratories. Of these specimens, 254 were reactive, and 610 were nonreactive with the ADVIA Centaur HSV2 assay. The overall agreement was 97.6% (843/864) with a 95% confidence interval (CI) of 96.3%–98.4%. Samples were analyzed in singlicate.
Of the 864 specimens tested by the Comparative Assay, 22 were equivocal and were further tested by the Western Blot test. After Western Blot testing, 20 of the 22 specimens were resolved to be negative and 2 remained equivocal.

The results obtained for the intended use population are presented below

Intended use population		Comparative Assay Equivocal results have been resolved by Western Blot (WB)			
		Positive	Negative	Equivocal	Total
ADVIA Centaur HSV2	Reactive	245	9	0	254
	Nonreactive	10	598	2	610
	Total	**255**	**607**	**2**	**864**

The sensitivity of the ADVIA Centaur HSV2 assay was 95.3% (245/257), with a 95% confidence interval (CI) of 92.0%–97.3%.

The specificity of the ADVIA Centaur HSV2 assay was 98.5% (598/607), with a 95% confidence interval (CI) of 97.2%–99.2%.

Sensitivity and specificity were determined for the pregnant population by comparing the performance of the ADVIA Centaur HSV2 assay to the Comparative Assay and Western Blot confirmatory method. The results of pregnant women samples are presented below:

Pregnant women Study Contingency (WB resolution) table

Pregnant women		**Comparative assay Equivocal results have been resolved by Western Blot (WB)**			
		Positive	**Negative**	**Equivocal**	**Total**
ADVIA Centaur HSV2	**Reactive**	34	4	0	38
	Nonreactive	0	236	0	236
	Total	34	240	0	274

The sensitivity of the ADVIA Centaur HSV2 assay was 100.0% (34/34) with a 95% confidence interval of 89.9%–100.0%.

The specificity of the ADVIA Centaur HSV2 assay was 98.3% (236/240) with a 95% confidence interval of 95.8%–99.4%.

10. Stability

The onboard stability of the ADVIA Centaur Herpes-2 IgG reagents is 60 days with a calibration interval of 28 days. The onboard stability of the ADVIA Centaur Herpes-2 IgG Calibrators is 8 hours. The opened vial stability of the ADVIA Centaur Herpes-2 IgG Calibrators is 65 days. Unopened reagents and calibrators are stable until the date printed on the box label when stored at 2-8°C.

11. Conclusion

The analytical and clinical study results demonstrate that the ADVIA Centaur Herpes-2 IgG are substantially equivalent to the predicate device, Focus HerpeSelect 1 and 2 Immunoblot IgG (FDA cleared under K000238), and that the assay is safe and effective for its labeled intended use.