

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number: K122979

B. Purpose for Submission: New device

C. Measurand: IgM antibodies to *Borrelia burgdorferi* proteins

D. Type of Test: Enzyme immunoassay

E. Applicant: bioMerieux SA

F. Proprietary and Established Names: VIDAS® Lyme IgM

G. Regulatory Information:

1. Regulation section: 21 CFR 866.3830; Treponema pallidum treponemal test reagents
2. Classification: Class II
3. Product code: LSR; Reagent, Borrelia Serological Reagent
4. Panel: Microbiology

H. Intended Use:

1. Intended use(s): The VIDAS Lyme IgM (LYM) assay is an automated qualitative enzyme immunoassay intended for use on the instruments of the VIDAS family in the presumptive detection of human IgM antibodies to *Borrelia burgdorferi* in human serum (plain or separation gel) or plasma (sodium heparin or lithium heparin). It should be used to test patients with a history and/or symptoms of infection with *B. burgdorferi*. All VIDAS Lyme IgM positive and equivocal specimens should be further tested with a Western Blot IgM assay to obtain supportive evidence of infection with *B. burgdorferi*.

2. Indication(s) for use: The VIDAS Lyme IgM (LYM) assay is an automated qualitative enzyme immunoassay intended for use on the instruments of the VIDAS family in the presumptive detection of human IgM antibodies to *Borrelia burgdorferi* in human serum (plain or separation gel) or plasma (sodium heparin or lithium heparin). It should be used to test patients with a history and/or symptoms of infection with *B. burgdorferi*. All VIDAS Lyme IgM positive and equivocal specimens should be further tested with a Western Blot IgM assay to obtain supportive evidence of infection with *B. burgdorferi*.

3. Special conditions for use statement(s): For prescription use
4. Special instrument requirements: VIDAS and miniVIDAS instruments

I. Device Description: The VIDAS Lyme IgM assay principle combines a 2-step enzyme immunoassay sandwich method with a final fluorescent detection (ELFA). The Solid Phase Receptacle (SPR®) serves as the solid phase as well as the pipetting device for the assay. Reagents for the assay are ready-to-use and predispensed in the sealed reagent strips. All of the assay steps are performed automatically by the instrument. The reaction medium is cycled in and out of the SPR several times.

After a preliminary wash step and a sample dilution step, the antibodies to *B. burgdorferi* present in the specimen will bind to the *B. burgdorferi* specific recombinant proteins coating the interior of the SPR. Unbound sample components are washed away. Anti-human IgM antibodies conjugated with alkaline phosphatase will attach to the immunocomplex bound to the SPR wall.

A final wash step removes unbound conjugate. During the final detection step, the substrate (4-Methyl-umbelliferyl phosphate) is cycled in and out of the SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone) the fluorescence of which is measured at 450 nm. The intensity of the fluorescence is proportional to the quantity of anti-*B.burgdorferi* IgM antibody present in the sample.

At the end of the VIDAS Lyme IgM assay, results are automatically calculated by the instrument. A test value is generated and a report is printed.

J. Substantial Equivalence Information:

1. Predicate device name(s): Platelia™ Lyme IgM
2. Predicate 510(k) number(s): K081362
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	The VIDAS Lyme IgM (LYM) assay is an automated qualitative enzyme immunoassay intended for use on the instruments of the VIDAS family in the presumptive detection of human IgM	The Platelia™ Lyme IgM Test is a qualitative test intended for use in the presumptive detection of human IgM antibodies to <i>Borrelia burgdorferi</i> in human serum or plasma (K3 EDTA, sodium

Similarities		
Item	Device	Predicate
	antibodies to <i>Borrelia burgdorferi</i> in human serum (plain or separation gel) or plasma (sodium heparin or lithium heparin). It should be used to test patients with a history and/or symptoms of infection with <i>B. burgdorferi</i> . All VIDAS Lyme IgM positive and equivocal specimens should be further tested with a Western Blot IgM assay to obtain supportive evidence of infection with <i>B. burgdorferi</i> .	heparin or sodium citrate). The EIA system should be used to test serum or plasma from patients with a history and symptoms of infection with <i>B. burgdorferi</i> . All positive and equivocal specimens should be re- tested with a specific, second-tier test such as Western Blot. Positive second- tier results are supportive evidence of infection with <i>B. burgdorferi</i> . The diagnosis of Lyme disease should be made based on history and symptoms (such as <i>erythema migrans</i>), and other laboratory data, in addition to the presence of antibodies to <i>B. burgdorferi</i> . Negative results (either first or second-tier) should not be used to exclude Lyme disease.
Specimen	Serum or plasma	Serum or plasma
Analyte	IgM antibodies to <i>Borrelia burgdorferi</i>	IgM antibodies to <i>Borrelia burgdorferi</i>
Method	Qualitative	Qualitative

Differences		
Item	Device	Predicate
Antigens	Recombinant proteins of <i>B. burgdorferi</i>	Whole cell extract of <i>B. burgdorferi</i> antigens

Differences		
Item	Device	Predicate
Assay Technique	Enzyme-linked fluorescent assay (ELFA)	Enzyme immunoassay (EIA)
Automated	Yes	No

K. Standard/Guidance Document Referenced (if applicable): Not applicable

L. Test Principle: Enzyme Immunoassay

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision: For the precision study, 4 serum samples were tested in duplicate in 40 different runs (2 runs per day over 20 days) with 2 reagent lots at 1 site (n = 80). The precision was calculated following the recommendations of the CLSI[®] document EP5-A2. The total precision data in the table reflect the 80 values generated per sample for Site 1 and takes into account replicate, run, day, calibration, and lot as potential sources of variation. The total precision for controls includes within-day, between-days and between-calibration variability and is lot specific.

Panel Member	N	Mean Index	Within-run		Within-day		Between-days		Total	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Sample 1	80	0.19	0.01	3.9	0.01	2.7	0.00	0.0	0.01	5.2
Sample 2	80	0.27	0.01	4.7	0.01	2.8	0.00	1.4	0.02	9.1
Sample 3	80	0.38	0.01	2.6	0.01	3.0	0.00	0.3	0.02	4.7
Sample 4	80	1.31	0.03	2.1	0.02	1.6	0.01	0.9	0.09	6.9
Positive Control	40	0.74	NA	NA	0.04	5.3	0.00	0.0	0.07	10.1
Negative Control	40	0.00	NA	NA	0.00	0.0	0.00	0.0	0.00	0.0

Reproducibility: For reproducibility, 4 serum samples were tested in duplicate in 40 different runs (2 runs per day over 20 days) with 2 reagent lots at 3 sites (n =240). The reproducibility was calculated following the recommendations of the CLSI® document EP5-A2. The total reproducibility data in the table reflects the 240 values generated per sample for all sites and takes into account replicate, run, day, calibration, lot, and site as potential sources of variation. Out of the 240 total values, 2 Low Positives (Sample 3) gave an equivocal value (< 0.32). The total reproducibility for controls includes within-day, between-days, between-calibration and between-site variability and is lot specific.

Panel Member	N	Mean Index	Within-run		Within-day		Between-days		Between-site		Total	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Sample 1	240	0.19	0.01	3.5	0.00	2.1	0.00	1.0	0.00	0.0	0.01	6.3
Sample 2	240	0.26	0.01	4.3	0.01	2.7	0.00	0.7	0.01	2.1	0.02	7.8
Sample 3	240	0.37	0.01	3.1	0.01	2.1	0.00	0.0	0.00	0.0	0.02	6.2
Sample 4	240	1.26	0.03	2.5	0.02	1.9	0.01	0.4	0.00	0.0	0.12	9.4
Positive Control	120	0.72	NA	NA	0.03	4.6	0.00	0.0	0.00	0.0	0.09	12.1
Negative Control	120	0.00	NA	NA	0.00	0.0	0.00	0.0	0.00	0.0	0.00	0.0

b. *Linearity/assay reportable range:* N/A

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):* N/A

d. *Detection limit:* N/A

e. *Analytical specificity:*

Testing asymptomatic population: 100 sera from apparently healthy subjects from an endemic population (New York) and 100 sera from a non-endemic population (Texas) with no known history of Lyme disease were run on the VIDAS Lyme IgM assay and the predicate Lyme IgM assay. The following results were obtained:

	VIDAS		Predicate	
	Positivity*	Negativity	Positivity*	Negativity
Endemic	12.0%	88.0%	19.0%	81.0%
Non-Endemic	14.0%	86.0%	3.0%	97.0%

* Includes positives and equivocal.

Cross-reactivity: Cross-reactivity is based on the study of samples that are negative with the test being evaluated and positive for the potentially interfering disease. The results of the samples tested according to the disease are shown in the table below:

Infection or Diagnosis	N	VIDAS Lyme IgM Equivocal or positive results	% Cross-reactivity
Anti Nuclear Antibodies	60	3	5.00
C Reactive Protein	61	4	6.55
Cytomegalovirus	34	6	17.64
Epstein Barr Virus	65	7	10.76
<i>Helicobacter pylori</i>	143	10	6.99
Hepatitis A Virus	153	22	14.37
Herpes Simplex Virus	98	15	15.30
Human Immunodeficiency Virus	20	7	35.00
Human Anti-mouse Antibodies	31	2	6.45
Leptospirosis	216	22	10.18
Measles	38	5	13.15
Mumps	46	2	4.34
Rheumatoid Factor	61	5	8.19
Rickettsiosis	112	6	5.35
Rubella	19	2	10.52
Syphilis	270	25	9.25
Systemic Lupus Erythematosus	28	2	7.14
Toxoplasmosis	26	5	19.23
Varicella Zoster Virus	58	4	6.89

The effect of Babesiosis, Ehrlichiosis and Rocky mountain spotted fever pathologies on the VIDAS Lyme IgM performance is not known.

Interfering Substances: Interferences were studied according to the recommendations of CLSI® document EP7-A2. None of the following factors have been found to significantly influence this assay:

- hemolysis (after spiking samples with hemoglobin: 5 g/L [monomer]),
- lipemia (after spiking samples with lipids: 30 g/L equivalent in triglycerides),
- bilirubinemia (after spiking samples with bilirubin: 0.3 g/L),
- human albumin (after spiking samples with albumin up to 60 g/L).

It is recommended not to use samples that are hemolyzed, lipemic or icteric and, if possible, to collect a new sample.

f. Assay cut-off: The clinical cut-off of the assay was determined using a Receiver Operating Characteristic (ROC) curve analysis. 211 negative sera and 211 positive sera were used to determine the cut-off value that gave the best discrimination between the sensitivity and the specificity of the assay. The cut-off index value for VIDAS Lyme IgM was determined to be equal to 0.12.

2. Comparison studies:

a. Method comparison with predicate device:

Method Comparison: A prospective study was performed on 975 fresh or frozen prospectively collected sera submitted for routine Lyme disease testing from an endemic area of the United States. Testing was performed in three laboratories. At each laboratory, the samples were tested in parallel using a commercially available Lyme IgM EIA method (predicate) and the VIDAS Lyme IgM assay. Positive % Agreement (PPA) is calculated for the positives and equivocals together since the 2-tier testing does not make a distinction and calls for both of them to be tested by Western Blot. Combined results from the three sites are shown below:

VIDAS Lyme IgM	Predicate Lyme IgM		
	Positive	Equivocal	Negative
Positive	71	10	32
Equivocal	15	11	55
Negative	50	53	678
Total	136	74	765

VIDAS Lyme IgM	Predicate Lyme IgM		
	Positive	Equivocal	Negative
Positive % Agreement 95% CI	51.0% (107/210) [44.0 - 57.9]%		
Negative % Agreement 95% CI	88.6% (678/765) [86.2 - 90.8]%		

Second-Tier Testing: In accordance with the CDC recommendations for use of a 2-tier Lyme disease testing scheme, the VIDAS Lyme IgM positive and equivocal results and the predicate Lyme IgM positive and equivocal results were confirmed using a commercially available Lyme IgM Western Blot method. The percent agreement between VIDAS and predicate Lyme IgM positives (1st tier PPA) and the percent agreement between VIDAS–predicate–Western Blot IgM positives and Predicate–Western Blot IgM positives (2nd tier PPA) are shown below.

	1 st Tier + or ±	IgM Western	
		Pos.	Neg.
Predicate IgM	210	104	106
VIDAS IgM	194	95	93*
VIDAS IgM and Predicate IgM	107	84	23

*, Western Blot results were not available for 6 of the positive or equivocal samples by VIDAS Lyme IgM assay.

Agreement results:

1st Tier PPA = 51.0% (107/210), 95% CI=[44.0% - 57.9%]
 2nd Tier PPA= 80.8% (84/104), 95% CI=[72.2% - 87.2%]

Concordance with IgM Western Blot:

Predicate device: 49.5% (104/210)
 VIDAS Lyme IgM: 49.0% (95/194)

b. Matrix comparison:

Matrix Equivalency: A matrix equivalency study for the claimed sample matrix types (serum and plasma) and tube types (a dry serum tube, a separation gel serum tube, a sodium heparinate plasma tube and a lithium heparinate plasma tube) was performed by testing thirty five samples with Index values covering the dynamic range of the assay. A 24% (2 x 12%) allowable total error was used when the VIDAS Lyme IgM index was > 0.10. At or below a 0.10 VIDAS Lyme IgM index, the allowable total error of 0.024 in terms of absolute difference was

used. A Passing-Bablok regression was used to compare the results of each sampling tube to the results of the reference tube, the dry serum tube. For all conditions, the proportional bias was < 12% and no sample exceeded the allowable total error. The comparison study results are shown below.

Passing-Bablok regression analysis

Tested conditions	Intercept (CI at 95%)	Slope (CI at 95%)
Separation gel serum tube / Dry serum tube	0.00 (-0.01 to 0.03)	1.00 (0.93 to 1.05)
Lithium Heparinate plasma tube / Dry serum tube	0.02 (-0.02 to 0.06)	1.01 (0.91 to 1.11)
Sodium Heparinate plasma tube / Dry serum tube	0.02 (-0.02 to 0.011)	1.00 (0.77 to 1.11)

The following table summarizes the results of the matrix equivalency study. The number and percentage (%) of specimens are reported for index differences between each sampling tube type and the reference tube.

Tested conditions	Number and percentage (%) of specimens		
	Index difference <10%	10% ≤ Index difference <20%	Index difference ≥20%
Separation gel serum tube	33/34 (97.0%)	1/34 (3.0%)	0/34 (0.0%)
Lithium Heparinate plasma tube	26/34 (76.4%)	7/34 (20.6%)	1/34 (3.0%)
Sodium Heparinate plasma tube	23/34 (67.6%)	10/34 (29.4%)	1/34 (3.0%)

3. Clinical studies:

a. *Clinical Sensitivity:*

Sensitivity: 202 retrospective samples from patients meeting a case definition of LD and confirmed positive for *B. Burgdorferi* infection were run on the VIDAS Lyme IgM assay and the predicate Lyme IgM assay. For both the VIDAS Lyme IgM and the predicate test, equivocal results were considered as positive for the evaluation. The following results were obtained:

Stage	N	VIDAS Lyme IgM % Sensitivity *	Predicate Lyme IgM % Sensitivity *	Difference in proportions
Stage I (early localized, single lesion) 1 – 30 days	119	52.1 (62/119) 95% CI [42.8 – 61.3]%	54.6 (65/119) 95% CI [45.2 – 63.8]%	-2.5% 95% CI [(-15.2)% – (10.2)%]
Stage II (early disseminated, multiple lesions) 1 – 30 days	62	91.9 (57/62) 95% CI [82.2 - 97.3]%	91.9 (57/62) 95% CI [82.2 – 97.3]%	0.0% 95% CI [(-9.6)% – (9.6)%]
Stage III (late disseminated)	21	76.2 (16/21) 95% CI [52.8 - 91.8]%	61.9 (13/21) 95% CI [38.4 – 81.9]%	14.3% 95% CI [(-13.3)% – (41.9)%]
All stages	202	66.8 (135/202) 95% CI [59.9 – 73.3]%	66.8 (135/202) 95% CI [59.9 – 73.3]%	0.0% 95% CI [(-9.2)% – (9.2)%]

* includes positive and equivocal results.

b. *Clinical specificity:* N/A

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

CDC Lyme panel: The following information is from a serum panel obtained from the CDC and tested using the VIDAS Lyme IgM kit. 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.

Time from onset	VIDAS Lyme IgM			Western blot IgM		
	Positive or equivocal	Negative	Agreement with clinical status	Positive	Negative	Agreement with clinical status
Normals	1	4	80.0 % (4/5)	0	5	100.0 % (5/5)
< 1 month	3	2	60.0 % (3/5)	3	2	60.0 % (3/5)
1 – 2 months	5	1	83.3 % (5/6)	5	1	83.3 % (5/6)
3- 12 months	12	4	75.0 % (12/16)	7	9	43.8 % (7/16)
> 1 year	3	4	42.9 % (3/7)	3	4	42.9 % (3/7)
Total	24	15	69.2% (27/39)	18	21	59.0 % (23/39)

5. Expected values/Reference range:

Expected values: The following tables summarize the expected (observed) values for the sensitivity, analytical specificity, and method comparison studies performed with VIDAS Lyme IgM assay.

Sensitivity study: The table below shows the results of testing with the VIDAS Lyme IgM assay (LYM) using a population of 202 patients with case-defined Lyme disease. This population was 65.3% male, 34.7% female with a mean age of 48 years. The VIDAS LYM test values ranged from 0.00 to 5.87 with overall positivity of 59.4%. The VIDAS Lyme IgM sensitivity for stage I samples increased with increasing duration of symptoms, with a positivity rate of 38.7% in the first week, but reaching 70.0% by week 4 of symptoms. The positivity rate for stage II samples reached 93.8% by week 2 of post-onset of symptoms. The positivity rate for stage III samples was 66.7%.

LYM Values – Sensitivity Study

Population	N	Days post-onset	Age (Mean)	% Male	% Female	Index Range	% Positive Results
Stage I: Single Lesion	62	1-7	48	58.1	41.9	[0.00-4.64]	38.7
	30	8-14	51	60.0	40.0	[0.00-5.18]	40.0
	17	15-21	46	58.8	41.2	[0.01-4.66]	52.9
	10	22-30	49	90.0	10.0	[0.09-5.06]	70.0
	119	Total	49	61.3	38.7	[0.00-5.18]	43.7
Stage II: Multiple Lesions	29	1-7	47	72.4	27.6	[0.03-5.77]	82.8
	16	8-14	47	75.0	25.0	[0.03-5.87]	93.8
	13	15-21	46	69.2	30.8	[0.28-5.71]	92.3
	4	22-30	41	100.0	0.0	[0.29-5.28]	75.0
	62	Total	46	74.2	25.8	[0.03-5.87]	87.6
Stage III: Late Disseminated	21	Total	49	57.1	42.9	[0.00-5.44]	66.7
All samples	202	Total	48	65.3	34.7	[0.00-5.87]	59.4

Analytical Specificity Study: The table below shows the results of testing with the LYM assay using a population of 200 apparently healthy individuals in the US. This population was 56.0% male, 44.0% female with a mean age of 35 years. Fifty percent (50%) of the samples were collected in a non-endemic area of the US and 50% in an endemic area. VIDAS LYM test values ranged from 0.00 to 0.72 with overall negativity of 87.0%.

LYM Values – Analytical Specificity

Population	N	Age (Mean)	% Male	% Female	Index Range	% Positive Results *
Endemic	100	30	55.0	45.0	[0.00-0.72]	12.0

Non-Endemic	100	41	57.0	43.0	[0.00-0.61]	14.0
All samples	200	35	56.0	44.0	[0.00-0.72]	13.0

* includes positive and equivocal results.

Method Comparison Study: The table below shows the results of a prospective study conducted in an endemic area of the US. This study included samples from 975 patients subjected to routine Lyme disease testing. The population was 44.9% male, 55.1% female with a mean age of 44 years. VIDAS LYM test values ranged from 0.00 to 6.14 with overall positivity of 13.9%.

LYM Values – Method Comparison

Population	N	Age (Mean)	% Male	% Female	Index Range	% Positive Results
Site 1	200	45	48.5	51.5	[0.00-5.52]	6.5
Site 2	434	44	43.3	56.7	[0.00-6.14]	14.5
Site 3	341	44	44.9	55.1	[0.00-5.48]	17.6
All samples	975	44	44.9	55.1	[0.00-6.14]	13.9

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.