

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

A. 510(k) Number: K122986

B. Purpose for Submission: New Device

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

D. Type of Test: Enzyme immunoassay

E. Applicant: bioMerieux

F. Proprietary and Established Names: VIDAS® Lyme IgG

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 IgG (LYG) assay is an automated qualitative enzyme immunoassay intended for use on the instruments of the VIDAS family in the presumptive detection of human IgG 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 IgG positive specimens should be further tested with a Western Blot IgG assay to obtain supportive evidence of infection with *B. burgdorferi*.

2. Indication(s) for use: The VIDAS Lyme IgG (LYG) assay is an automated qualitative enzyme immunoassay intended for use on the instruments of the VIDAS family in the presumptive detection of human IgG 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 IgG positive specimens should be further tested with a Western Blot IgG 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 IgG assay principle combines a 2-step enzyme immunoassay sandwich method with a final fluorescent detection (ELFA) (see User’s Manual). 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 IgG 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* IgG antibody present in the sample.

At the end of the VIDAS Lyme IgG 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 IgG
2. Predicate 510(k) number(s): K080012
3. Comparison with predicate:

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

| Similarities | | |
|--------------|---|--|
| Item | Device | Predicate |
| | detection of human IgG 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 IgG positive specimens should be further tested with a Western Blot IgG assay to obtain supportive evidence of infection with <i>B. burgdorferi</i> . | (K3 EDTA, sodium 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 | IgG antibodies to <i>Borrelia burgdorferi</i> | IgG antibodies to <i>Borrelia burgdorferi</i> |
| Method | Qualitative | Qualitative |

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

| Differences | | |
|-----------------|---|---|
| Item | Device | Predicate |
| Assay Technique | <i>B. burgdorferi</i> Enzyme-linked fluorescent assay (ELFA) | <i>burgdorferi</i> antigens 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: 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 IgG assay and the predicate Lyme IgG assay. The following results were obtained:

| | VIDAS | | Predicate | |
|--------------------|------------|------------|---------------------------|------------|
| | Positivity | Negativity | Positivity ⁽¹⁾ | Negativity |
| Endemic | 3.0% | 97.0% | 3% | 97.0% |
| Non-Endemic | 0.0% | 100.0% | 1% | 99.0% |

⁽¹⁾ Includes positives and equivocal results..

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 between-run, between-day 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 (%) |

| | | | | | | | | | | |
|-------------------------|----|------|------|------|------|-----|------|-----|------|------|
| Negative | 80 | 0.11 | 0.01 | 9.7 | 0.00 | 3.8 | 0.01 | 5.4 | 0.02 | 18.5 |
| High Negative | 80 | 0.15 | 0.02 | 11.2 | 0.01 | 5.3 | 0.00 | 0.0 | 0.03 | 18.3 |
| Low Positive | 80 | 0.26 | 0.01 | 4.3 | 0.01 | 3.8 | 0.01 | 2.4 | 0.02 | 6.8 |
| High Positive | 80 | 2.34 | 0.09 | 3.7 | 0.05 | 2.3 | 0.07 | 3.0 | 0.13 | 5.7 |
| Positive Control | 40 | 0.45 | NA | NA | 0.03 | 5.9 | 0.01 | 1.4 | 0.03 | 6.7 |
| 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 high negatives gave a positive value and 2 low positives gave a negative value. The total reproducibility for controls include 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 (%) |
| Negative | 240 | 0.11 | 0.01 | 7.6 | 0.00 | 4.3 | 0.00 | 3.8 | 0.00 | 0.0 | 0.02 | 15.5 |
| High Negative | 240 | 0.15 | 0.01 | 8.6 | 0.00 | 3.3 | 0.00 | 0.0 | 0.00 | 0.0 | 0.02 | 15.5 |
| Low Positive | 240 | 0.26 | 0.01 | 5.4 | 0.01 | 3.9 | 0.00 | 1.6 | 0.00 | 0.0 | 0.02 | 7.7 |
| High Positive | 240 | 2.31 | 0.10 | 4.1 | 0.04 | 1.8 | 0.03 | 1.2 | 0.02 | 0.8 | 0.12 | 5.3 |
| Positive Control | 120 | 0.45 | NA | NA | 0.02 | 5.2 | 0.00 | 0.0 | 0.00 | 0.0 | 0.03 | 6.3 |
| Negative Control | 120 | 0.00 | NA | NA | 0.00 | 0.00 | 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:*

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 IgG positive results | % Cross-reactivity |
|------------------------------|-----|---------------------------------|--------------------|
| Anti Nuclear Antibodies | 60 | 5 | 8.33 |
| C Reactive Protein | 61 | 2 | 3.28 |
| Cytomegalovirus | 40 | 0 | 0.00 |
| Epstein Barr Virus | 34 | 0 | 0.00 |
| <i>Helicobacter pylori</i> | 143 | 2 | 1.40 |
| Hepatitis A Virus | 150 | 3 | 2.00 |
| Herpes Simplex Virus | 125 | 1 | 0.80 |
| Human Immunodeficiency Virus | 20 | 1 | 5.00 |
| Human Anti-mouse Antibodies | 43 | 0 | 0.00 |
| Leptospirosis | 206 | 6 | 2.91 |
| Measles | 38 | 0 | 0.00 |
| Mumps | 46 | 0 | 0.00 |
| Rheumatoid Factor | 28 | 0 | 0.00 |
| Rickettsiosis | 133 | 3 | 2.25 |
| Rubella | 19 | 0 | 0.00 |
| Syphilis | 256 | 1 | 0.39 |
| Systemic Lupus Erythematosus | 28 | 2 | 7.14 |
| Toxoplasmosis | 26 | 1 | 3.85 |
| Varicella Zoster Virus | 58 | 0 | 0.00 |

The effect of Babesiosis, Ehrlichiosis and Rocky mountain spotted fever pathologies on the VIDAS Lyme IgG 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 (hemoglobin: 5 g/L (monomer)),
- lipemia (lipids: 30 g/L equivalent in triglycerides),

- bilirubinemia (bilirubin: 0.3 g/L),
- human albumin (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. 268 negative sera and 250 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 value for VIDAS Lyme IgG was determined to be equal to 0.20.

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 IgG EIA method (predicate) and the VIDAS Lyme IgG 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 IgG | Predicate Lyme IgG | | |
|--|-------------------------------------|-----------|----------|
| | Positive | Equivocal | Negative |
| Positive | 77 | 17 | 36 |
| Negative | 18 | 15 | 812 |
| Total | 95 | 32 | 848 |
| Positive % Agreement 95% CI | 74.0 % (94/127) [65.5% - 81.4%] | | |
| Negative % Agreement 95% CI | 95.8 % (812/848) [94.2% - 97.0%] | | |

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

| | 1 st Tier + or ± | <u>IgG Western</u> | |
|--------------------------------|--------------------------------|--------------------|------|
| | | Pos. | Neg. |
| Predicate IgG | 127 | 63 | 64 |
| VIDAS IgG | 130 | 65 | 65 |
| VIDAS IgG and Predicate IgG | 94 | 62 | 32 |

1st tier PPA = 74.0 % (94/127) [95% CI; 65.5% - 81.4%]

2nd tier PPA = 98.4% (62/63) [95% CI; 91.47 – 99.96]

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 IgG index was > 0.10. At or below a 0.10 VIDAS Lyme IgG 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 | -0.04 (-0.10 to 0.00) | 1.02 (0.97 to 1.07) |
| Lithium Heparinate plasma tube / Dry serum tube | -0.11 (-0.17 to -0.03) | 1.05 (1.00 to 1.10) |
| Sodium Heparinate plasma tube / Dry serum tube | -0.04 (-0.14 to -0.01) | 1.03 (0.99 to 1.08) |

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 | 30/35 (85.7%) | 5/35 (14.3%) | 0/35 (0.0%) |

| | | | |
|--------------------------------|------------------|-----------------|----------------|
| Lithium Heparinate plasma tube | 29/35 (82.9%) | 4/35 (11.4%) | 2/35 (5.7%) |
| Sodium Heparinate plasma tube | 28/35 (80.0%) | 7/35 (20.0%) | 0/35 (0.0%) |

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 IgG assay and the predicate Lyme IgG assay. For the predicate test, equivocal results were considered as positive for the evaluation. The following results were obtained:

| Stage | N | VIDAS Lyme IgG % Sensitivity | Predicate Lyme IgG % Sensitivity | Difference in proportions |
|--|-----|--|----------------------------------|----------------------------------|
| Stage I (early localized, single lesion) 1 – 30 days | 119 | 49.60 95% CI ⁽¹⁾ [40.3% – 58.9%] | 42.90 95% CI [33.8% – 52.3%] | +6.7% 95% CI [(-6)% – (19)%] |
| Stage II (early disseminated, multiple lesions) 1 – 30 days | 61 | 83.60 95% CI [71.9% – 91.8%] | 54.10 95% CI [40.8% – 66.9%] | +29.5% 95% CI [(14)% – (45)%] |
| Stage III (late disseminated) | 22 | 90.90 95% CI [70.8% – 98.9%] | 72.70 95% CI [49.8% – 89.3%] | +18.2% 95% CI [(-4)% – (40)%] |
| All stages | 202 | 64.40 95% CI [57.3% – 71.0%] | 49.50 95% CI [42.4% – 56.6%] | +14.9% 95% CI [(5)% – (24)%] |

⁽¹⁾ 95% Confidence Interval.

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 IgG 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 IgG | | | Western Blot IgG | | |
|----------------------|----------------|----------|--------------------------------|------------------|----------|--------------------------------|
| | Positive | Negative | Agreement with clinical status | Positive | Negative | Agreement with clinical status |
| Normals | 0 | 5 | 100.0 % (5/5) | 0 | 5 | 100.00 % (5/5) |
| < 1 month | 2 | 3 | 40.0 % (2/5) | 2 | 3 | 40.00 % (2/5) |
| 1 – 2 months | 4 | 2 | 66.6 % (4/6) | 0 | 6 | 0.00 % (0/6) |
| 3 - 12 months | 8 | 8 | 50.0 % (8/16) | 7 | 9 | 43.75% (7/16) |
| > 1 year | 7 | 0 | 100.0 % (7/7) | 7 | 0 | 100.00 % (7/7) |
| Total | 21 | 18 | 66.6 % (26/39) | 16 | 23 | 53.84% (21/39) |

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 IgG assay.

Sensitivity study: The table below shows the results of testing with the VIDAS Lyme IgG assay (LYG) 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 LYG test values ranged from 0.01 to 8.86 with overall sensitivity of 64.4%. The VIDAS Lyme IgG sensitivity for stage I samples increased with increasing duration of symptoms, with a positivity rate of 35.5% in the first week, but reaching 80.0% by week 4 of symptoms. The positivity rate for stage II samples reached 100% by week 2 of post-onset of symptoms. The positivity rate for stage III samples was 90.9%.

LYG 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% | [0.01-8.86] | 35.5% |
| | 30 | 8-14 | 51 | 60.0% | 40.0% | [0.02-5.99] | 56.7% |
| | 17 | 15-21 | 46 | 58.8% | 41.2% | [0.04-7.51] | 70.6% |

| | | | | | | | |
|---|-----|-------|----|--------|-------|-------------|--------|
| | 10 | 22-30 | 49 | 90.0% | 10.0% | [0.01-6.25] | 80.0% |
| | 119 | Total | 49 | 61.3% | 38.7% | [0.01-8.86] | 49.6% |
| Stage II: Multiple Lesions | 29 | 1-7 | 47 | 72.4% | 27.6% | [0.01-7.39] | 65.5% |
| | 16 | 8-14 | 47 | 75.0% | 25.0% | [0.23-8.31] | 100.0% |
| | 12 | 15-21 | 46 | 75.0% | 25.0% | [1.14-7.44] | 100.0% |
| | 4 | 22-30 | 41 | 100.0% | 0.0% | [0.39-5.33] | 100.0% |
| | 61 | Total | 46 | 75.4% | 24.6% | [0.01-8.31] | 83.6% |
| Stage III: Arthritis, Neuroborreliosis | 22 | Total | 50 | 59.1% | 40.9% | [0.02-8.16] | 90.9% |
| All samples | 202 | Total | 48 | 65.3% | 34.7% | [0.01-8.86] | 64.4% |

Analytical Specificity Study: The table below shows the results of testing with the LYG 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 LYG test values ranged from 0.00 to 1.33 with overall negativity of 98.5%.

LYG Values – Analytical Specificity

| Population | N | Age (Mean) | % Male | % Female | Index Range | % Positive Results |
|-------------|-----|------------|--------|----------|-------------|--------------------|
| Endemic | 100 | 30 | 55.0% | 45.0% | [0.00-1.33] | 3.0% |
| Non-Endemic | 100 | 41 | 57.0% | 43.0% | [0.01-0.15] | 0.0% |
| All samples | 200 | 35 | 56.0% | 44.0% | [0.00-1.33] | 1.5% |

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 LYG test values ranged from 0.00 to 9.18 with 13.3% positive samples.

LYG Values – Method Comparison

| Population | N | Age (Mean) | % Male | % Female | Index Range | % Positive Results |
|------------|-----|------------|--------|----------|-------------|--------------------|
| Site 1 | 200 | 45 | 48.5% | 51.5% | [0.00-5.09] | 5.5% |
| Site 2 | 434 | 44 | 43.3% | 56.7% | [0.00-9.18] | 14.5% |

| | | | | | | |
|--------------------|-----|----|-------|-------|-------------|-------|
| Site 3 | 341 | 44 | 44.9% | 55.1% | [0.00-8.99] | 16.4% |
| All samples | 975 | 44 | 44.9% | 55.1% | [0.00-9.18] | 13.3% |

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.