

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

**A. 510(k) Number:**

K093678

**B. Purpose for Submission:**

To expand the Intended Use Statement to include Bronchoalveolar Lavage (BAL) Fluid samples

**C. Measurand:**

*Aspergillus* galactomannan antigen

**D. Type of Test:**

Enzymatic immunoassay

**E. Applicant:**

Bio-Rad Laboratories

**F. Proprietary and Established Names:**

Bio-Rad Laboratories Platelia™ *Aspergillus* EIA

**G. Regulatory Information:**

1. Regulation section:

21 CFR 866.3040 *Aspergillus spp.*, Serological Reagents

2. Classification:

Class I

3. Product code:

NOM - Antigen, Galactomannan, *Aspergillus spp.*

4. Panel:

83 - Microbiology

## **H. Intended Use:**

### **1. Intended use:**

The Platelia™ Aspergillus EIA is an immunoenzymatic sandwich microplate assay for the detection of Aspergillus galactomannan antigen in adult and pediatric serum and bronchoalveolar lavage (BAL) fluid samples.

The Platelia™ Aspergillus EIA is a test which, when used in conjunction with other diagnostic procedures such as microbiological culture, histological examination of biopsy samples and radiographic evidence, can be used as an aid in the diagnosis of Invasive Aspergillosis.

### **2. Indication(s) for use:**

The Platelia™ Aspergillus EIA is an immunoenzymatic sandwich microplate assay for the detection of Aspergillus galactomannan antigen in adult and pediatric serum and bronchoalveolar lavage (BAL) samples

The Platelia™ Aspergillus EIA is a test which, when used in conjunction with other diagnostic procedures such as microbiological culture, histological examination of biopsy samples and radiographic evidence, can be used as an aid in the diagnosis of Invasive Aspergillosis.

### **3. Special conditions for use statement(s):**

For prescription use only

### **4. Special instrument requirements:**

Microplate reader equipped with 450 nm & 620/630 nm filters

## **I. Device Description:**

The device consists of an EIA kit containing a microwell strip plate and reagents. Each plate consists of 12 strips of 8 wells each. Each well is coated with an anti-galactomannan monoclonal antibody. Reagents include wash solution, negative, positive and cut-off control sera, conjugate, treatment solution, substrate buffer, chromogen and stopping solution.

## **J. Substantial Equivalence Information:**

### **1. Predicate device name(s):**

Platelia™ Aspergillus EIA

### **2. Predicate 510(k) number(s):**

K023857 (no pediatric claim)

K060641 (pediatric claim)

### 3. Comparison with predicate:

| Similarities        |                                                                                                                                                    |                     |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Item                | New Device (K093678)                                                                                                                               | Predicate (K060641) |
| Analyte             | Galactomannan antigen Detection                                                                                                                    | Same                |
| Intended Use        | Detection of <i>Aspergillus</i> galactomannan antigen in adult and pediatric serum samples.                                                        | Same                |
| Reagents/Components | Conjugate, Wash Buffer, Substrate, TMB Chromogen, Sample Diluent, Positive Control, Stop Solution., 96 well microplate –antibody coated microwells | Same                |
| Incubation Temp.    | 37°C                                                                                                                                               | Same                |
| Incubation Time     | 90 ± 5 minutes                                                                                                                                     | Same                |

| Differences  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                            |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Item         | New Device (K093678)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Predicate (K060641)                                                                        |
| Intended Use | Detection of galactomannan antigen in adult and pediatric serum and Bronchoalveolar Lavage (BAL) Fluid samples                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Detection of <i>Aspergillus</i> galactomannan antigen in adult and pediatric serum samples |
| Matrix       | Bronchoalveolar Lavage (BAL) Fluid samples                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Serum                                                                                      |
| Limitations  | <p><u>Limitation 1:</u> Addition of Histoplasma and Geotrichum to the list of fungi causing cross- reactivity</p> <p><u>Limitation 2:</u> Addition of a limitation that cross-reactivity of BAL fluid with Mycoplasma and anaesthetic drugs used to numb the neck/throat area has not been evaluated</p> <p><u>Limitation 3:</u> Addition of a limitation regarding positive reactions observed in patients receiving products containing sodium gluconate, galactofuranose or galactomannan.</p> <p>Limitation 4 Addition of a limitation regarding positive reactions observed in patients receiving PLASMALYTE™ solution.</p> <p>Limitation 5 Addition of a limitation that assay results in BAL fluid samples from immunocompromised patients should be interpreted with caution.</p> |                                                                                            |

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

EP-15A2: CLSI User Verification of Performance for Precision and Trueness. (June 2005)

## **L. Test Principle:**

The Platelia™ Aspergillus EIA is a one-stage immunoenzymatic sandwich microplate assay that detects galactomannan in human serum. The assay uses rat EBA-2 monoclonal antibodies, which are directed against Aspergillus galactomannan, and have been characterized in previous studies. The monoclonal antibodies are used to coat the wells of the microplate and bind the antigen and to detect the antigen bound to the sensitized microplate (conjugate reagent: peroxidase-linked monoclonal antibodies). Serum samples are heat-treated in the presence of EDTA in order to dissociate immune complexes and to precipitate serum proteins that could possibly interfere with the test. The treated serum samples and conjugate are added to the wells coated with monoclonal antibodies, and incubated. A monoclonal antibody-galactomannan monoclonal antibody/peroxidase complex is formed in the presence of galactomannan antigen. The strips are washed to remove any unbound material. Next, the substrate solution is added, which will react with the complexes bound to the well to form a blue color reaction. The enzyme reaction is stopped by the addition of acid, which changes the blue color to yellow. The absorbance (optical density) of specimens and controls is determined with a spectrophotometer set at 450 and 620/630 nm wavelength.

## **M. Performance Characteristics (if/when applicable):**

### **I. Analytical performance:**

#### **a. *Precision/Reproducibility:***

##### **Reproducibility Studies in BAL**

Inter and Intra-Assay variability was determined using a panel of four pooled patient BAL fluid samples spiked with purified galactomannan (one negative, one high negative, one low positive and one medium positive) at two external clinical sites (US) and one internal site (France). Platelia™ Aspergillus EIA positive and negative kit controls were included as panel members. Each of the four panel members and two controls were tested in duplicate on two runs per day on five different days, on one lot, (total replicates at each site =120). Two operators performed all the precision testing at each site. The total number of replicates combining all three sites was 60 per panel member and 360 total test results.

Intra-assay reproducibility was defined by the within-run variance of the mean optical density (OD) and Index. Inter-assay reproducibility was defined by the total variance of the mean optical density (OD) and Index. Total variance in this design will be the sum of the between-day, between-run, between operator, between-site and within-run variance components. The percent coefficient of variation (CV %) was defined as the standard deviation divided by the mean concentration.

The sample size (n), mean optical density (OD) and Index, standard deviation (SD) and percent coefficient of variation (CV %) for each panel member were calculated according to the recommendations described in the Clinical and Laboratory Standards Institute (CLSI) EP15-A2 Evaluation Protocol and the ISO/TR 22971 Technical Report Site

Results were as follows:

| Summary                  |     | Negative |       | High Negative |       | Low Positive |        | Medium Positive |       | Positive Control |        | Negative Control |       |
|--------------------------|-----|----------|-------|---------------|-------|--------------|--------|-----------------|-------|------------------|--------|------------------|-------|
|                          |     | N= 60    |       | N=59*         |       | N=59*        |        | N=60            |       | N=60             |        | N=60             |       |
|                          |     | OD       | Index | OD            | Index | OD           | Index  | OD              | Index | OD               | Index  | OD               | Index |
| Mean                     |     | 0.121    | 0.29  | 0.210         | 0.49  | 0.370        | 0.87   | 0.575           | 1.35  | 1.580            | 3.72   | 0.047            | 0.11  |
| Within Run (Intra Assay) | SD  | N/A      | N/A   | 0.016         | 0.037 | 0.032        | 0.073% | 0.029           | 0.067 | 0.111            | 0.265  | N/A              | N/A   |
|                          | %CV | N/A      | N/A   | 7.7%          | 7.4%  | 8.7%         | 8.4%   | 5.0%            | 5.0%  | 7.0%             | 7.1%   | N/A              | N/A   |
| Total (Inter Assay)      | SD  | N/A      | N/A   | 0.046         | 0.096 | 0.052        | 0.101  | 0.070           | 0.138 | 0.190            | 0.438  | N/A              | N/A   |
|                          | %CV | N /A     | N/A   | 22.1%         | 22.1% | 14.0%        | 11.6%  | 12.2 %          | 10.2% | 12.0%            | 11.8 % | N/A              | N/A   |

\*One statistical outlier was removed from the analysis.

b. *Linearity/assay reportable range:*

N/A

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

#### Quality Control

**Cut-off Control:** The OD of each Cut-off Control Serum must be:

$$\geq 0.300 \text{ and } \leq 0.800$$

**Positive Control:** The index of the Positive Control Serum must be greater than 2.00.

$$I = \frac{\text{OD. Positive Control (R5)}}{\text{Mean Cut-off Control OD}} > 2.00$$

**Negative Control:** The index of the Negative Control Serum must be less than 0.40.

$$I = \frac{\text{OD. Negative Control (R3)}}{\text{Mean Cut-off Control OD}} < 0.40$$

Failure of any of the controls to meet the validity criteria described above renders the assay invalid, and patient specimen results should not be reported. The operator may decide to repeat the assay, after reviewing the procedure, or may contact the manufacturer for assistance. If a repeat assay is performed, then a new aliquot of the same sample should be used in the repeat assay.

## Stability

Freeze/thaw studies were performed with this assay to validate four freeze/thaw cycles for Bronchoalveolar Lavage (BAL) fluid samples.

Three *Aspergillus* Galactomannan antigen negative [Low Negative (<0.1 Index), Negative (0.1-0.2 Index) and High Negative (0.2-0.4 Index)] and two *Aspergillus* Galactomannan antigen positive [(low positive (0.5-1.5 Index), and high positive (> 2.5 Index)] patient BAL fluid samples were tested based on results from testing after thawing the selected BAL samples.

The index values of the BAL patient samples after the initial thawing above were used as reference results for the freeze/thaw study comparison. Three further freeze/thaw cycles were studied. Upon testing after thawing, the results were slightly lower than the original test results. This is not unusual in that the original results were tested at a different time and different kit lot and index values (not quantitative) can change. Therefore, the method was revised on testing the BAL samples after the first thaw. The revised sample ranges were low negative, negative, high negative, positive and high positive. Each BAL sample was aliquotted and labeled in eight tubes, each at 300 µL per tube (two tubes for each of 4 time points) and subjected to freeze-thaw treatment. Results showed that the mean index values and the percent recovery for each sample and freeze/thaw tested compared well to the mean of the four reference (first thaw) results. In addition, the three negative samples remained negative throughout the study and there was no significant change in the index value for each of them. The two positive samples had percent recovery values that were within the acceptance criteria for the study protocol (reference index +20%). In conclusion, freeze/thaw cycles do not appear to have any adverse affect on the *Aspergillus* galactomannan samples.

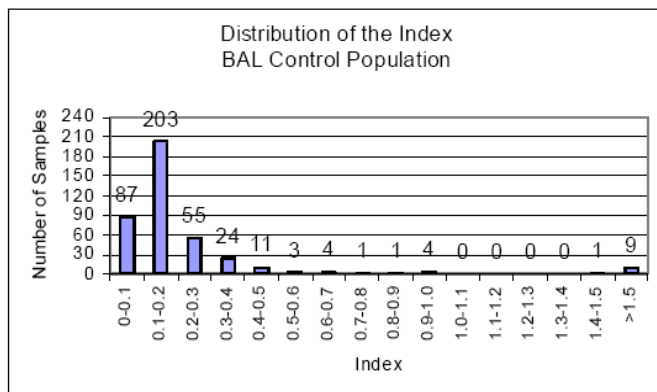
## Expected Values

The expected prevalence of Invasive Aspergillosis varies with the patient population; rates from 5-20% have been reported. The following results have been obtained from clinical studies conducted on pediatric (age ≤ 21 years) patients in the United States and on adult patients in North America.

### BAL Samples

Two US studies were conducted on a total of 449 BAL samples from 178 Solid Organ transplant (SOT) and lung transplant recipients with and without invasive aspergillosis to determine the performance characteristics of the Platelia™ *Aspergillus* EIA kit with Bronchoalveolar Lavage Fluid samples. Of these, there were 403 BAL samples from 167 solid organ and lung transplant recipients without invasive aspergillosis. Results were as follows:

### Combined SOT and Lung Transplant Recipients without Invasive Aspergillosis Control Populations N =403 BAL Fluids



Expected values in BAL samples from the combined SOT and lung transplant recipients without Invasive Aspergillosis are presented in the Table below. Results are presented by samples from transplant recipients with and without mold colonization.

### Expected Values by Sample Combined SOT and Lung Transplant Recipients without Invasive Aspergillosis N =403 BAL Fluids

| Diagnosis                     | N   | Positive (%) | Negative (%)   |
|-------------------------------|-----|--------------|----------------|
| Controls without colonization | 341 | 11/341(3.2%) | 330/341(96.8%) |
| Controls with colonization    | 62  | 12/62(19.4%) | 50/62(80.6%)   |
| Control Total                 | 403 | 23/403(5.7%) | 380/403(94.3%) |

Expected values in BAL samples from the combined SOT and lung transplant recipients without Invasive Aspergillosis are presented by transplant type in the table below.

### Expected Values by Sample Combined SOT and Lung Transplant Recipients without Invasive Aspergillosis By Transplant Type N =403 BAL Fluids

| Diagnosis     | N    | Positive (%) | Negative (%)   |
|---------------|------|--------------|----------------|
| Heart         | 28   | 3/28(10.7%)  | 25/28(89.3%)   |
| Kidney        | 6225 | 3/25(12.0%)  | 22/25(88.0%)   |
| Liver         | 23   | 1/23(4.3%)   | 22/23(95.7%)   |
| Lung          | 327  | 16/327(4.9%) | 311/327(95.1%) |
| Control Total | 403  | 23/403(5.7%) | 380/403(94.3%) |

Values ranged from approximately 3 – 19 % which corresponds with the 5-20% expected values.

*d. Detection limit:*

N/A

*e. Analytical specificity:*

A study to evaluate the effect of potentially interfering medical conditions unrelated to Invasive Aspergillosis was performed with one lot of the Platelia™ *Aspergillus* EIA kit. The following **serum** samples were tested for cross-reactivity with the Platelia™ *Aspergillus* EIA. A total of 151 **sera** were tested. Results were as follows:

| Pathology                                                            | # Samples Tested | # Positives |
|----------------------------------------------------------------------|------------------|-------------|
| Rheumatoid Factor                                                    | 10               | 0           |
| ANA Positive                                                         | 10               | 0           |
| IgG Hypergammaglobulinemia                                           | 10               | 0           |
| IgM Hypergammaglobulinemia                                           | 10               | 0           |
| Cancer*                                                              | 11               | 0           |
| Non-Viral Cirrhosis (primary biliary; alcohol induced; drug induced) | 10               | 0           |
| Multiple Transfusions                                                | 10               | 0           |
| Multiparous Females                                                  | 10               | 0           |
| HAV                                                                  | 10               | 0           |
| HCV                                                                  | 10               | 0           |
| Rubella                                                              | 10               | 0           |
| CMV                                                                  | 10               | 0           |
| Syphilis (RPR+)                                                      | 10               | 0           |
| Toxoplasmosis                                                        | 10               | 0           |
| Mycoplasma                                                           | 10               | 0           |

BAL

Cross-reactivity studies using BAL fluid were not performed for this assay. The EDTA/heat treatment of the samples precipitates the proteins and only the supernatant is used for testing. Galactomannan is not affected in this process since it is heat-resistant.

A limitation has been added to the Package Insert as follows:

“Cross-reactivity of BAL fluid samples with Mycoplasma or anaesthetic drugs/lubricants used to numb the neck/throat area for the aspiration process has not been evaluated.”

*f. Assay cut-off*

The cut-off studies for this assay with BAL fluid have not been performed for this assay. The clinical studies included in this submission were conducted using the 0.5 cut-off recommended in the package insert for the current product.

2. Comparison studies:

*a. Method comparison with predicate device:*

Not applicable

b. *Matrix comparison:*

Not applicable

3. Clinical studies:

a. *Clinical Sensitivity:*

Sensitivity was evaluated in Solid Organ Transplant and lung transplant recipients diagnosed with invasive aspergillosis according to the EORTC/MSG criteria.

- i. Solid Organ Transplant recipients with Invasive Aspergillosis:  
Of the total of 116 samples from 62 Solid Organ Transplant recipients in one study in the United States, sensitivity was evaluated using the Platelia™ *Aspergillus* EIA in 5 Solid Organ Transplant recipients with invasive aspergillosis.

**Sensitivity with Bio-Rad Platelia™ *Aspergillus* EIA Proven or Probable Invasive Aspergillosis in Solid Organ Transplant Recipients By Patient**

| Diagnosis                                  | Number of Patients | Sensitivity | 95% Confidence Interval |
|--------------------------------------------|--------------------|-------------|-------------------------|
| Proven Aspergillosis                       | 2                  | 100% (2/3)  | 34.2 – 100%             |
| Probable Aspergillosis                     | 3                  | 100% (3/3)  | 43.8 – 100%             |
| Combined Proven and Probable Aspergillosis | 5                  | 100% (5/5)  | 56.5 – 100%             |

**Sensitivity with Bio-Rad Platelia™ *Aspergillus* EIA Proven or Probable Invasive Aspergillosis in Solid Organ Transplant Recipients By Sample**

| Diagnosis                                  | Number of Patients | Sensitivity   | 95% Confidence Interval |
|--------------------------------------------|--------------------|---------------|-------------------------|
| Proven Aspergillosis                       | 11                 | 36.4% (4/11)  | 15.2 – 64.6%            |
| Probable Aspergillosis                     | 7                  | 85.7% (6/7)   | 46.8 – 97.4%            |
| Combined Proven and Probable Aspergillosis | 18                 | 55.6% (10/18) | 33.7 – 75.5%            |

- ii. Lung Transplant Recipients with Invasive Aspergillosis:

A total of 116 consecutive lung transplant recipients undergoing bronchoscopy at the Universities of Pittsburgh Medical Center for surveillance or suspected

organ rejection were prospectively enrolled BALs from 2 patients with proven IA, 19 BALs from 4 patients with probable IA.

**Sensitivity with Bio-Rad Platelia™ *Aspergillus* EIA Proven or Probable Invasive Aspergillosis in Lung Transplant Recipients By Patient**

| Diagnosis                                  | Number of Patients | Sensitivity | 95% Confidence Interval |
|--------------------------------------------|--------------------|-------------|-------------------------|
| Proven Aspergillosis                       | 2                  | 50% (1/2)   | 9.4 – 90.6%             |
| Probable Aspergillosis                     | 4                  | 75% (3/4)   | 30.0 – 96.4%            |
| Combined Proven and Probable Aspergillosis | 6                  | 66.7% (4/6) | 30.0 – 90.3%            |

**Sensitivity with Bio-Rad Platelia™ *Aspergillus* EIA Proven or Probable Invasive Aspergillosis in Lung Transplant Recipients By Sample**

| Diagnosis                                  | Number of Patients | Sensitivity  | 95% Confidence Interval |
|--------------------------------------------|--------------------|--------------|-------------------------|
| Proven Aspergillosis                       | 9                  | 22.2% (2/9)  | 6.3 – 54.8%             |
| Probable Aspergillosis                     | 19                 | 36.8% (7/19) | 19.1 – 59.0%            |
| Combined Proven and Probable Aspergillosis | 28                 | 32.1% (9/28) | 17.9 – 50.7%            |

iii. Combined Solid Organ and Lung Transplant Recipients with IA:

**Sensitivity with Bio-Rad Platelia™ *Aspergillus* EIA Proven or Probable Invasive Aspergillosis in Solid Organ Transplant and Lung Transplant Recipients By Patient**

| Diagnosis                                  | Number of Patients | Sensitivity  | 95% Confidence Interval |
|--------------------------------------------|--------------------|--------------|-------------------------|
| Proven Aspergillosis                       | 4                  | 75.0% (3/4)  | 30.0 – 95.4%            |
| Probable Aspergillosis                     | 7                  | 85.7% (6/7)  | 48.6 – 97.4%            |
| Combined Proven and Probable Aspergillosis | 11                 | 81.8% (9/11) | 52.3 – 94.9%            |

**Sensitivity with Bio-Rad Platelia™ *Aspergillus* EIA Proven or Probable Invasive Aspergillosis in Solid Organ Transplant and Lung Transplant Recipients By Sample**

| Diagnosis            | Number of Patients | Sensitivity  | 95% Confidence Interval |
|----------------------|--------------------|--------------|-------------------------|
| Proven Aspergillosis | 20                 | 30.0% (6/20) | 14.5 – 51.9%            |

|                                            |    |               |              |
|--------------------------------------------|----|---------------|--------------|
| Probable Aspergillosis                     | 26 | 50.0% (13/26) | 32.0 – 68.0% |
| Combined Proven and Probable Aspergillosis | 46 | 41.3% (19/46) | 28.3– 55.7%  |

iv. Hematologic disease patients with invasive aspergillosis

Sensitivity was also evaluated in 58 samples from 58 hematologic disease patients diagnosed with invasive aspergillosis as shown in the table below. In the study a retrospective analysis was performed on BAL samples from high risk hematology patients using the Platelia™ *Aspergillus* EIA. The data from this published study below was evaluated to establish the performance characteristics of the Platelia™ *Aspergillus* EIA on BAL fluid.

*Maertens et al. 2009 Bronchoalveolar Lavage Fluid Galactomannan for the Diagnosis of Invasive Pulmonary Aspergillosis in Patients with Hematologic Diseases. Clin. Infect. Dis.*49:1688-93

**Proven or Probable Invasive Aspergillosis in Hematologic Disease Patients**

| <b>Diagnosis</b>                           | <b>N</b> | <b>Index <math>\geq 0.5</math></b> | <b>Sensitivity</b> | <b>95% Confidence Interval</b> |
|--------------------------------------------|----------|------------------------------------|--------------------|--------------------------------|
| Proven Aspergillosis                       | 31       | 31                                 | 31/31 (100%)       | 89.0 - 100%                    |
| Probable Aspergillosis                     | 27       | 26                                 | 26/27 (96.3%)      | 81.7 - 99.3%                   |
| Combined Proven and Probable Aspergillosis | 58       | 57                                 | 57/58 (98.3%)      | 90.8 - 99.7%                   |

*b. Clinical Specificity*

Specificity was evaluated in a total of 98 samples from 57 SOT recipients and 305 samples from 110 lung transplant recipients entered into the studies that were not diagnosed with Invasive Aspergillosis during the evaluation period. Specificity is defined as a negative (Index < 0.5) Bio-Rad Platelia™ *Aspergillus* EIA result in a BAL fluid from a patient without Invasive Aspergillosis. Specificity in BAL samples from the combined SOT and lung transplant recipients without Invasive Aspergillosis is presented in the table below. Results are presented by samples from transplant recipients with and without mold colonization.

Specificity in BAL samples from the combined SOT and lung transplant recipients without Invasive Aspergillosis is presented in the following tables .

**Specificity by Sample Combined SOT and Lung Transplant Recipients without Invasive Aspergillosis N = 403 BAL Fluids**

| Diagnosis                    | Number of Samples | Specificity     | 95% Confidence Interval |
|------------------------------|-------------------|-----------------|-------------------------|
| Control without colonization | 341               | 96.8% (330/341) | 94.3 – 98.2%            |
| Controls with colonization   | 50                | 80.6% (50/62)   | 69.1 – 88.6%            |
| Control Total                | 403               | 94.3% (380/403) | 91.6– 96.2%             |

**Specificity by Patient Combined SOT and Lung Transplant Recipients without Invasive Aspergillosis N = 167 Transplant Recipients**

| Diagnosis                    | Number of Samples | Specificity     | 95% Confidence Interval |
|------------------------------|-------------------|-----------------|-------------------------|
| Control without colonization | 119               | 90.8% (108/119) | 84.2 – 94.8%            |
| Controls with colonization   | 48                | 79.2% (38/48)   | 65.7 – 88.3%            |
| Control Total                | 167               | 87.4% (146/167) | 81.5– 91.6%             |

Specificity was also evaluated in a total of 41 BAL samples from 41 hematologic disease patients without IA. Results are shown in the table below

**Specificity by Sample  
Hematologic Disease Patients without Invasive Aspergillosis  
N= 41**

| Diagnosis        | N  | Index < 0.5 | Negative (%)  | 95% Confidence Interval |
|------------------|----|-------------|---------------|-------------------------|
| Control Patients | 41 | 33          | 33/41 (80.5%) | 66.0 – 89.8%            |

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

4. Clinical cut-off:

N/A

5. Expected values/Reference range:

Positive and negative predictive values have been analyzed for the patient population in this study. Based on the actual average of 13.6% prevalence rate in pediatrics and 16.9% prevalence rate in adults observed in this study, positive and negative predictive values have been calculated as below:

**Pediatrics**

Study Prevalence 13.6%

PPV: 39.1% 95% Confidence Interval : 22.2-59.2%

NPV: 92.2% 95% Confidence Interval : 85.3-96.0%

**Adults**

Study Prevalence 16.9%

PPV: 59.0% 95% Confidence Interval:43.4-72.9%

NPV: 95.5% 95% Confidence Interval: 90.5-97.9%

The expected prevalence of Invasive Aspergillosis varies with the patient population; rates from 5-20% have been reported<sup>10, 24</sup>. For patient populations on the lower end of the published prevalence, the positive and negative prevalence have been re-calculated using a 5% prevalence rate.

**Pediatrics**

Calculated Prevalence 5%

PPV : 17.6% 95% Confidence Interval : 6.5-39.8%

NPV : 97.2% 95% Confidence Interval : 92.1-99.1%

**Adults**

Calculated Prevalence 5%

PPV: 27.2% 95% Confidence interval: 13.7-46.7%

NPV: 98.8% 95% Confidence Interval: 95.4-99.7%

**N. Proposed Labeling:**

The proposed labeling is sufficient and satisfies the requirements of 21 CFR section 809.10

**O. Conclusion:**

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