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K023857

MAY 16 2003

ATTACHMENT I **510(k) SUMMARY**

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is K023857.

DATE:	May 7, 2003
APPLICANT:	Bio-Rad 3, Boulevard Raymond Poincaré 92430 Marnes-la-Coquette, France
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PRODUCT TRADE NAME:	Bio-Rad Laboratories Platelia® *Aspergillus* EIA
COMMON NAME:	*Aspergillus* Antigen EIA
CLASSIFICATION NAME:	*Aspergillus* spp. serological reagents
PREDICATE DEVICE:	Meridian Premier Cryptococcal Antigen

DEVICE DESCRIPTION

The Platelia *Aspergillus* EIA is a one-stage immunoenzymatic sandwich microplate assay which detects galactomannan in human serum. The assay uses the rat monoclonal antibody EBA-2, which is directed against *Aspergillus* galactomannan, and has been characterized in previous studies[7, 11]. The monoclonal antibody is used: to coat the wells of the microplate and bind the antigen, and as the detector antibody in the conjugate reagent (peroxidase-linked monoclonal antibody).

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 antibody, and incubated. A monoclonal antibody - galactomannan - monoclonal antibody / peroxidase complex is formed in the presence of *Aspergillus* 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 optical absorbance of specimens and controls is determined with a spectrophotometer set at 450 and 620/630 nm wavelength.

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INTENDED USE

The Platelia® *Aspergillus* EIA is an immunoenzymatic sandwich microplate assay for the detection of *Aspergillus* galactomannan antigen in serum.

INDICATIONS FOR USE

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.

TECHNOLOGICAL CHARACTERISTICS

The following tables summarize similarities and differences between the Platelia® *Aspergillus* EIA and the Premier Cryptococcal Antigen EIA.

Table 1(a:) Similarities between reagents and materials

Similarities in Components / Materials	**Platelia® *Aspergillus* EIA, Catalog 62793**	**Premier Cryptococcal Antigen EIA, Catalog #602096**
Microplate	96 well microplate – antibody coated microwells	96 well microplate – antibody coated microwells
Reagents	Conjugate, Wash Buffer, Substrate, TMB Chromogen, Sample Diluent, Positive Control, Stop Solution.	Conjugate, Wash Buffer, Substrate, TMB Chromogen, Sample Diluent, Positive Control, Stop Solution.

Table 1(b): Differences between reagents and materials

Differences in Components / Materials	**Platelia® *Aspergillus* EIA, Catalog 62793**	**Premier Cryptococcal Antigen EIA, Catalog #602096**
Reagents	Negative and Cut-Off Controls, Specimen Treatment Solution	N/A

Table 2(a): Similarities between reagents with regard to function and use

Similarities in Function and Use	**Platelia® *Aspergillus* EIA, Catalog 62793**	**Premier Cryptococcal Antigen EIA, Catalog #602096**
Intended Use	Antigen detection	Antigen detection

Table 2(b): Differences between reagents with regard to function and use

Differences in Function and Use	**Platelia® *Aspergillus* EIA, Catalog 62793**	**Premier Cryptococcal Antigen EIA, Catalog #602096**
Intended Use	Qualitative detection of *Aspergillus* galactomannan antigen.	Qualitative and semi-quantitative detection of *Cryptococcal neoformans* capsular polysaccharide antigens.
Matrices	Serum	Serum and cerebrospinal fluid

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PERFORMANCE SUMMARY

A. Reproducibility Studies

Inter-assay and Intra-assay variability for the Platelia® *Aspergillus* EIA were determined in a study using a panel of 6 pooled patient serum samples (one negative, one low positive, two positive, and two high positive) obtained from actual clinical trial sites. Each of the 6 panel members were tested in triplicate (x3) on 3 different days, on 1 lot, at 2 sites (total number of replicates at each site = 9). Each of the 6 panel members was tested in duplicate (x2) on 3 different days, on 1 lot, at a third site (total number of replicates at the third site = 6). One (1) operator performed all precision testing at each site. The data was analyzed according to the National Committee for Clinical Laboratory Standards (NCCLS). The mean optical density (OD) and mean index value, standard deviation (SD), percent coefficient of variation (%CV), within lot precision (intra-assay) and within site (inter-assay) precision for each panel member at each site are illustrated below in the following tables.

Site 1

Panel Member	Neg		Low Pos		Pos #1		Pos #2		High Pos#1		High Pos #2		Neg Control		CO Control		Pos Control	
	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index
N	9	9	9	9	9	9	9	9	9	9	9	9	3	3	6	6	3	3
Mean	0.052	0.09	0.445	0.74	0.702	1.17	0.931	1.563	1.227	2.06	2.887	4.83	0.046	0.08	0.606	1.00	2.216	3.67
Within Run (intra-assay)[1] SD	0.002	0.00	0.022	0.03	0.059	0.09	0.044	0.08	0.051	0.09	0.089	0.17	N/A	N/A	0.02	0.03	N/A	N/A
%CV	N/A	N/A	4.8%	4.4%	8.4%	7.6%	4.7%	5.1%	4.2%	4.4%	3.1%	3.6%	N/A	N/A	3.7%	3.4%	N/A	N/A
Total (inter-assay)[2] SD	0.036	0.04	0.051	0.08	0.070	0.14	0.044	0.25	0.058	0.29	0.169	0.58	N/A	N/A	0.102	0.03	0.317	0.12
%CV	N/A	N/A	11.5%	10.4%	10.0%	11.6%	4.7%	15.7%	4.7%	14.3%	5.9%	11.9%	N/A	N/A	16.9%	2.8%	14.3%	3.3%

Site2

Panel Member	Neg		Low Pos		Pos #1		Pos #2		High Pos#1		High Pos #2		Neg Control		CO Control		Pos Control	
	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index
N	9	9	9	9	9	9	9	9	9	9	9	9	3	3	6	6	3	3
Mean	0.040	0.10	0.280	0.70	0.364	0.89	0.602	1.49	0.801	2.01	1.361	3.43	0.074	0.18	0.415	1.00	1.197	2.97
Within Run (intra-assay)[1] SD	0.006	0.01	0.041	0.09	0.023	0.07	0.045	0.11	0.046	0.10	0.047	0.11	N/A	N/A	0.00	0.01	N/A	N/A
%CV	N/A	N/A	14.5%	13.0%	6.4%	7.6%	7.5%	7.1%	5.7%	4.8%	3.5%	3.2%	N/A	N/A	1.1%	1.1%	N/A	N/A
Total (inter-assay)[2] SD	0.006	0.03	0.058	0.19	0.083	0.18	0.057	0.28	0.042	0.53	0.079	1.00	N/A	N/A	0.094	0.01	0.068	0.54
%CV	N/A	N/A	20.8%	27.0%	22.7%	19.8%	9.5%	18.7%	5.3%	26.5%	5.8%	29.2%	N/A	N/A	22.7%	0.9%	5.7%	18.2%

Site 3

Panel Member	Neg		Low Pos		Pos #1		Pos #2		High Pos#1		High Pos #2		Neg Control		CO Control		Pos Control	
	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index	OD	Index
N	6	6	6	6	6	6	6	6	6	6	6	6	3	3	6	6	3	3
Mean	0.049	0.10	0.388	0.81	0.652	1.36	0.830	1.73	1.158	2.41	2.378	4.96	0.059	0.12	0.480	1.00	1.652	3.45
Within Run (intra-assay)[1] SD	0.003	0.01	0.009	0.02	0.082	0.17	0.068	0.14	0.094	0.20	0.126	0.25	N/A	N/A	0.028	0.06	N/A	N/A
%CV	N/A	N/A	2.4%	2.4%	12.5%	12.2%	8.2%	8.2%	8.1%	8.2%	5.3%	5.1%	N/A	N/A	5.8%	5.8%	N/A	N/A
Total (inter-assay)[2] SD	0.012	0.03	0.078	0.13	0.068	0.15	0.104	0.25	0.082	0.15	0.111	0.34	N/A	N/A	0.028	0.04	0.056	0.23
%CV	N/A	N/A	20.0%	15.8%	10.5%	11.1%	12.5%	14.3%	7.1%	6.2%	4.7%	6.8%	N/A	N/A	5.8%	4.1%	3.4%	6.6%

N/A = not applicable

[1]NCCLS EP5-A, Vol. 19, No. 2, Page 24, Equation (C2)
[2]NCCLS EP5-A, Vol. 19, No. 2, Page 25, Equation (C3) and Equation (C4)

B. Cross Reactivity

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.

Pathology	**# Samples Tested**	**# Positives**
Rheumatoid Factor	10	0
ANA Positive	10	0
IgG Hypergammaglobulinemia	10	0
IgM Hypergammaglobulinemia	10	0
Cancer*	13	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

* One each of adenocarcinoma, bladder, breast(2), colon, endometrial, lung, melanoma (metastatic), prostate, renal, and squamous(3).

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C. Clinical Testing

Clinical testing to evaluate the sensitivity, specificity, and predictive value of the Platelia® Aspergillus EIA was conducted at three sites located in the U.S. and Canada. The study was conducted retrospectively using a total of 1890 serum samples collected from 179 patients from the following populations*:

- patients without signs of Invasive Aspergillosis (control patients)
- patients with probable Invasive Aspergillosis
- patients with proven Invasive Aspergillosis

* The Invasive Fungal Infection Cooperative Group (IFICG) of the European Organization for Research (EORTC) and the Mycosis Study Group (MSG of the National Institute of Allergy and Infectious Diseases (NIAID) have defined criteria for diagnosis of Invasive Aspergillosis (IA) in patients with hematologic malignancy or hematopoietic stem cell transplant.

Proven Invasive Aspergillosis is defined by positive microbiological culture obtained by sterile procedure from the site affected, and histopathological demonstration of the appropriate morphological forms in a host with symptoms attributed to the fungal infection.

*Probable Invasive Aspergillosis is defined as at least one microbiological criterion, **and** one major or two minor clinical criteria from a site consistent with infection, in a host with symptoms attributed to the fungal infection.*

*Possible Invasive Aspergillosis is defined as at least one microbiological criterion, **or** one major or two minor clinical criteria from a site consistent with infection, in a host with symptoms attributed to the fungal infection*

Given the relative rarity of Probable and Proven Invasive Aspergillosis, we offer the following definition of clinical sensitivity and specificity for the purposes of this study.

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SENSITIVITY

Results from this study have been analyzed in terms of patient sensitivity. Sensitivity testing was conducted using the Platelia® Aspergillus EIA at three sites on a combined total of 31 Bone Marrow Transplant (BMT) and Leukemia patients diagnosed with Proven or Probable Invasive Aspergillosis.

1. Proven Aspergillosis (as defined by IFICG / EORTC ; see above)

Combined Sites **N = 11 (patients)**

11 patients:
6 patients diagnosed with Proven Invasive Aspergillosis of the lung
5 patients diagnosed with Proven Invasive Aspergillosis of the sinus

Sensitivity : 81.8% (9 / 11).

Note : The 95% confidence interval could not be calculated due to insufficient sample size.

2. Probable Aspergillosis (as defined by IFICG / EORTC ; see above)

Combined Sites **N = 20 (patients)**

20 patients :
16 patients diagnosed with Probable Invasive Aspergillosis of the lung
4 patients diagnosed with Probable Invasive Aspergillosis of the sinus

Sensitivity : 80.0% (16 / 20).

Note : The 95% confidence interval could not be calculated due to insufficient sample size.

3. Combined Proven and Probable Aspergillosis (as defined by IFICG / EORTC ; see above)

Combined Sites **N = 31 (patients)**

31 patients:
22 patients diagnosed with Proven or Probable Invasive Aspergillosis of the lung
9 patients diagnosed with Proven or Probable Invasive Aspergillosis of the sinus

Sensitivity : 80.7% (25 / 31). The 95% confidence interval is 64.0 – 97.3%.

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SPECIFICITY

Specificity testing was conducted using the Platelia® Aspergillus EIA at three sites on a combined total of 1362 samples obtained from 148 Bone Marrow Transplant (BMT) and Leukemia patients without signs of Invasive Aspergillosis (control patients).

Site 1 **N = 33 patients**

449 sera obtained from:
16 BMT patients without signs of Invasive Aspergillosis
11 BMT patients colonized with *Aspergillus* and/or *Candida sp.*
1 BMT patient diagnosed with Invasive Fusariosis
3 BMT patients diagnosed with Candidemia
1 patient with blood cultures positive for *Lecythophora mutabilis*
1 patient diagnosed with Invasive *Pseudoallescheria boydii*

Site 1	**Specificity**	**95% Confidence Interval**
Patients (27/33)	81.8%	66.1 – 97.5%
Patients after repeat testing (31/33)		

Site 2 **N = 77 patients**

560 sera obtained from:
67 Leukemic patients without signs of Invasive Aspergillosis
8 Leukemic patients with Fungemia (*Candida, Fusarium, Trichosporon,* or *Aureobasidium*)
1 Leukemic patient diagnosed with Probable *Fusarium* pneumonia
1 Leukemic patient diagnosed with *Candida* pneumonia

Site 2	**Specificity**	**95% Confidence Interval**
Patients (71/77)	93.4%	87.1 – 99.8%
Patients after repeat testing (74/77)		

Site 3 **N = 38 patients**

353 sera obtained from :
28 BMT patients without signs of Invasive Aspergillosis
5 Leukemic patients receiving a second course of cytotoxic therapy
5 BMT patients being treated for Graft Versus Host Disease

Site 3	**Specificity**	**95% Confidence Interval**
Patients (34/38)	89.5%	77.8 – 100%
Patients after repeat testing (38/38)		

Combined Sites N = 148 patients*

Combined Sites	**Specificity**	**95% Confidence Interval**
Patients (132/148)	89.2%	83.8 – 94.6%
Patients after repeat testing (143/148)		

*Note: A total of 1343 sera obtained from 148 patients were tested. 1343 of the 1362 sera were initially negative, resulting in a sample agreement of 98.6% with a 95% confidence interval of 97.9 – 99.3%. On repeat testing, 1355 of the 1362 sera were negative.

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PREDICTIVE VALUE

Positive and negative predictive values have been analyzed for the patient population in this study, based on the actual average14% prevalence rate observed in this study. Positive and negative predictive values have been calculated for both the initial test result and after repeat testing.

Actual Prevalence of 14%	**PPV**	**NPV**
Patient	54.8 %	96.6 %
Patient after repeat testing	68.3 %	95.5 %

The expected prevalence of Invasive Aspergillosis varies with the patient population; rates from 5-20% have been reported[2,5]. 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.

Calculated Prevalence of 5%	**PPV**	**NPV**
Patient	12.5 %	96.0 %
Patient after repeat testing	31.3 %	96.3 %

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.

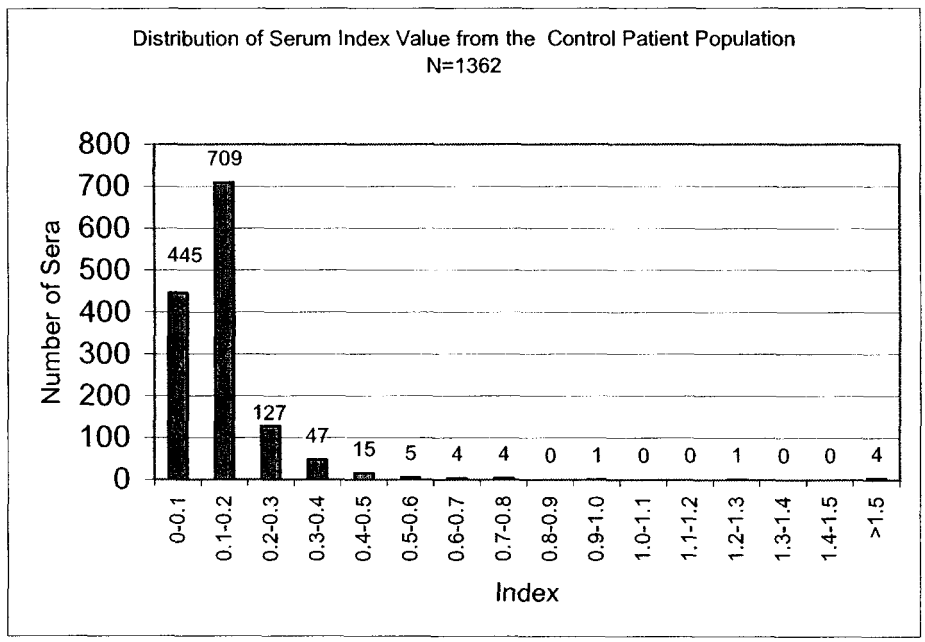
Pathology	**# Samples Tested**	**# Positives**
Rheumatoid Factor	10	0
ANA Positive	10	0
IgG Hypergammaglobulinemia	10	0
IgM Hypergammaglobulinemia	10	0
Cancer*	13	0
Non-Viral Cirrhosis (primary biliary; alcohol induced; drug induced)	10	0
Multiple Transfusions	10	0
Multiparous Females	10	0
HAV	10	0
HCV	10	0
Rubella	10	0
CMV	10	0
Syphilis (RPR+)	10	0
Toxoplasmosis	10	0
Mycoplasma	10	0

* One each of adenocarcinoma, bladder, breast(2), colon, endometrial, lung, melanoma (metastatic), prostate, renal, and squamous(3).

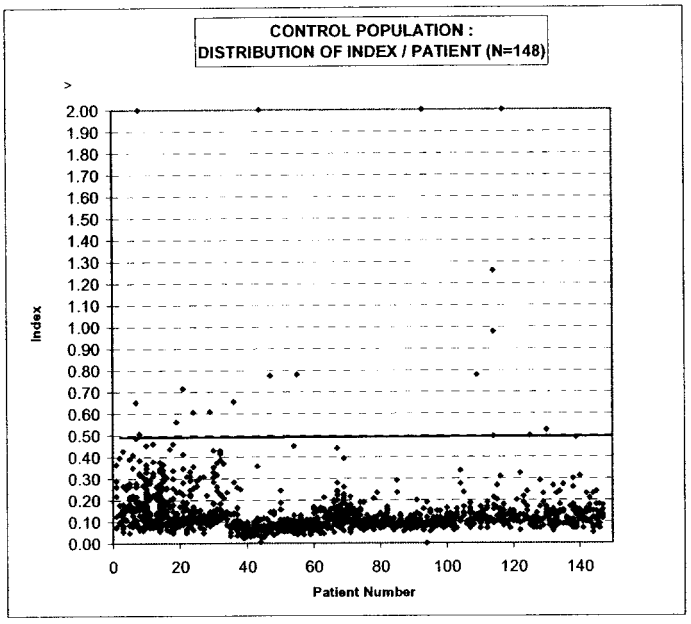
D. Expected Values

The expected prevalence of Invasive Aspergillosis varies with the patient population; rates from 5-20% have been reported[2,5]. A clinical study was conducted on a total of 1890 serum samples from 179 bone marrow transplant (BMT) and leukemic patients diagnosed with and without Invasive Aspergillosis, at three testing centers in North America to determine the performance characteristics of the Platelia® *Aspergillus* EIA. The average prevalence rate for this study was 14%. The distribution of index values for these populations is represented in the following charts.

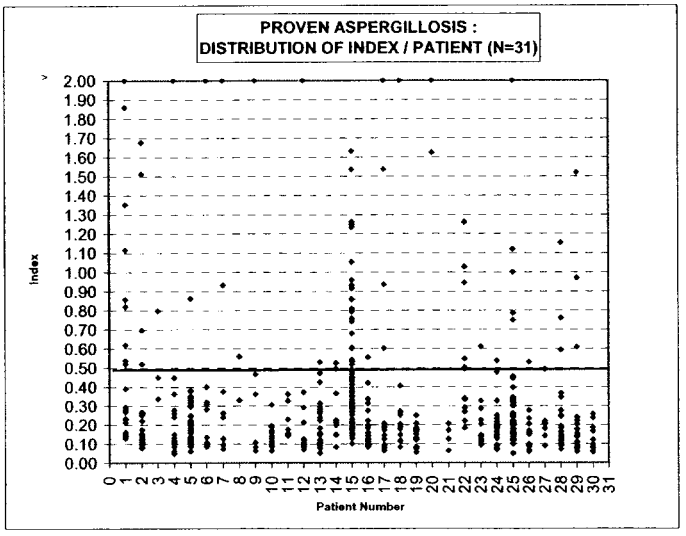
Patients diagnosed without Invasive Aspergillosis (control population)
A total of 1362 frozen serum samples obtained from 148 bone marrow transplant (BMT) and leukemic patients at three testing centers in North America were tested with the Platelia® Aspergillus EIA test. The distribution of index values is shown in the following chart.



This scatter plot depicts galactomannan assay results for the 1362 serum samples from 148 control patients in this study diagnosed (patients undergoing immunosuppressive therapy for HSCT, or to treat hematological malignancy).

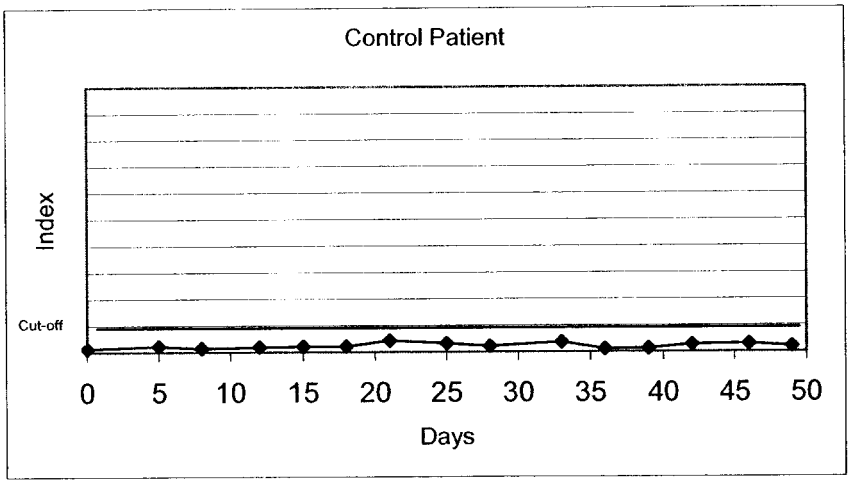


This scatter plot depicts galactomannan assay results for the 528 serum samples from 31 patients in this study diagnosed with proven or probable Invasive Aspergillosis as defined by EORTC/NIAID definitions. Not every serum sample from each patient is expected to be positive. The expected prevalence of Invasive Aspergillosis varies with the patient population; rates from 5-20% have been reported[2,5]. The prevalence rate for this study was 14%.

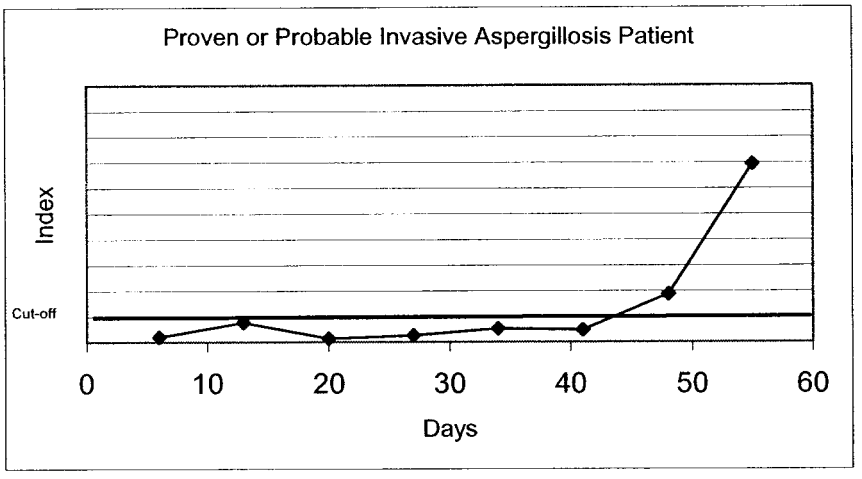


The following graphs represent examples of a patient without clinical signs or symptoms of Invasive Aspergillosis (negative for *Aspergillus*) and a patient with proven or probable Invasive Aspergillosis (positive for *Aspergillus*) respectively.

Negative Patient



Positive Patient



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E. Bibliography

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Re: k023857
Trade/Device Name: Platelia® Aspergillus EIA
Regulation Number: 21 CFR 866.3040
Regulation Name: Aspergillus Spp. Serological Reagents
Regulatory Class: Class I
Product Code: NOM
Dated: March 17, 2003
Received: March 18, 2003

Dear Mr. Bhend:

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. 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.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. 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 Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 594-3084. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

ATTACHMENT G INDICATIONS FOR USE STATEMENT

510(k) Number (if known): K023857

Device Name: Platelia® *Aspergillus* EIA

Indications for Use:

The Platelia® *Aspergillus* EIA is an immunoenzymatic sandwich microplate assay for the detection of *Aspergillus* galactomannan antigen in serum.

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.

(PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Professional Use: ✓

OR

Prescription Use: ✓
(Per 21 CFR 801.109)

Over-The-Counter Use: _____
(Optional Format 1-2-96)

Freddie M. Poole
Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) K023857