510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION

A. 510(K) NUMBER: K041002

B. ANALYTE:

Celiac IgA is designed for the simultaneous detection of human IgA isotype autoantibodies directed against Gliadin and Tissue Transglutaminase Enzyme.

Celiac IgG is designed for the detection of human IgG isotype autoantibodies directed against Gliadin.

C. TYPE OF TEST:

The **FIDIS™ Celiac** kit is a quantitative homogeneous fluorescent-based microparticles immunoassay using flow cytometry readings.

D. APPLICANT:

Biomedical Diagnostics S.A (bmd)
Actipole, 25-Bd de Beaubourg
BP 103
77423 Marne-La-Vallée Cedex 2
FRANCE.

E. PROPRIETARY AND ESTABLISHED NAMES:

FIDIS™ Celiac

F. REGULATORY INFORMATION:

1. *Regulation section:*

   21 CFR 866.5660 Multiple Autoantibodies Immunological Test System
2. *Classification:*

   Class II
3. *Product Code:*

   MST
   MVM
4. *Panel:*

   Immunology and Microbiology Devices

G. INTENDED USE:

The FIDIS™ Celiac kit is a semi-quantitative homogeneous fluorescent-based micro particles immunoassay using flow cytometry readings.

Celiac IgA is designed for the simultaneous detection of human IgA isotype antibodies directed against Gliadin and Tissue Transglutaminase Enzyme.

Celiac IgG is designed for the detection of human IgG isotype antibodies directed against Gliadin.

The presence of these antibodies can be used in conjunction with clinical findings to aid in the diagnosis of Celiac disease.

The FIDIS™ Celiac kit is to be used on serum only.

FIDIS™ Celiac kits are to be used on FIDIS™ Analyser, software and washer.

For in vitro diagnostic use.

H. GENERAL DESCRIPTION OF THE DEVICE:

FIDIS™ Celiac is based on Luminex 100™ Technology.

The Luminex technology (LabMAP™, Laboratory Multi-Analyte Profiling) is a unique system based on the association of microspheres, flow cytometer, high speed digital signal processor and an X-Y platform for reading 96-well microtiter plates facilitating automated sample acquisition. This combination allows the diagnostic of multiple biological analytes simultaneously.

This multiplexed microsphere-based flow cytometric assay involves fluorescent polystyrene microspheres. The antigen-coated microspheres are mixed and incubated with sample containing the analytes to be detected. A fluorochrome-conjugated detection molecule is subsequently incubated for analyte quantification.

The flow cytometer is equipped with a powerful digital signal processor and two lasers. A red "classification" laser, excites fluorescent molecules intrinsic embedded to the microspheres and a green "reporter" laser, excites the extrinsic fluochrome (Phycoerythrin or Alexa-532nm) bound to the microsphere surface.

During the sample reading, the flow cytometer analyzes individual microsphere, first, by size, and, second, by fluorescence emissions. Digital signal processors and computers algorithms provide simultaneous real-time acquisition of classification and reporter fluorescence signals output from the microspheres. Upon excitation, the emitted fluorescent signal from the microspheres travels through the optics paths to the individual detectors. According to the fluorescence ratio detected by the red laser, each microsphere is classified into on the basis of its unique fluorescence intensity which allows identifying which analyte is being tested. At the same time, the green "reporter" laser beam excites the external second molecule fluorescence to quantify the specific reaction related to each analyte.

Each antigen required for the assay is covalently coupled to an individual set of microspheres through its surface functional groups. The different antigen coupled microspheres are mixed together to constitute the final microspheres reagent. Celiac IgA allows the detection of anti-gliadin and anti-tissue transglutaminase IgA isotype antibodies. Celiac IgG allows the detection of anti-gliadin IgG isotype antibodies.

The test is performed in a 96 wells blank microplate including a filtering membrane at the bottom of the wells. In the first step, the sample is distributed in duplicate for the 2 isotypes (IgA and IgG) selected in each well containing respectively the Celiac A microspheres mixture, for the IgA isotype and the Celiac G microspheres mixture for the IgG isotype. After incubation, a wash step through a filtration process will eliminate the unbound antibodies.A specific conjugate consisting of either anti-human IgA or IgG antibodies coupled to phycoerythrin, is added to the mixture. It will bind to the previously captured antibodies.

The reaction is then directly measured by the flow cytometer, which categorizes each microspheres set according to its fluorescence colour the microspheres while simultaneously measuring the average fluorescence emitted by the conjugate. A calibration system allows expressing by interpolation the titer of the sample for each antibody specificity using a specific software developed by bmd.

The mixed and antigen-coated microspheres are first incubated with the sample to be analyzed. After the washing step, a phycoerythrin (PE)-labelled secondary anti-human IgA conjugate is added for antibodies quantifications at the surface of each microsphere set.

The microspheres are classified on the basis of their unique fluorescence intensity ratio that allows the identity of analyte being tested. Each dot in a white plot corresponds to an individual microsphere.

I. SUBSTANTIAL EQUIVALENCE INFORMATION:

Predicate device name(s):
BINDAZYME™ ELISA Human Anti Gliadin IgG Kit
BINDAZYME™ ELISA Human Anti Gliadin IgA Kit
BINDAZYME™ ELISA Human Anti Tissue Transglutaminase IgA Kit

Predicate K number(s):
K981929, K981929 and K993612

Comparison with predicate:

Item	Predicate devices	Current device
Intended use	Determination of IgG and IgA antibodies against gliadin and of IgA antibodies against tTG in human serum	Same
Antigens	Gliadin, tTG	Same
Washing	Yes	Same
Assay type	ELISA	fluorescent-based microparticles immunoassay using flow cytometry
Assay format	Individual assays	Individual assay for IgG and multiplexed assay for IgA
Solid phase	Microtiter plate	Colored-code microspheres sets
Reporter conjugate	HR peroxidase	Phycoerythrin
Substrate solution	TMB	None
Detection method	Colorimetry	Fluorescence
Reading	Spectrophotometer	Flow cytometer

J. TEST PRINCIPLE:

FIDIS™ Celiac is based on the use of distinct uniform size code-colored microspheres and a benchtopflow cytometer interfaced to a digital signal processing hardware and software. A red diode laser beam of the flow cytometer classifies each set of microspheres on the basis of its unique fluorescence intensity (red to orange), which allows identifying which analyte is being tested.

At the same time, a green laser beam illuminates the external second molecule fluorescence to quantify the specific reaction related to each analyte.

Each antigen required for the assay is covalently coupled to an individual set of microspheres through its surface functional groups. The different antigen coupled microspheres are mixed together to constitute the final microspheres reagent. Celiac IgA allows the detection of anti-gliadin and anti-tissue transglutaminase IgA isotype autoantibodies. Celiac IgG allows the detection of anti-gliadin IgG isotype autoantibodies.

The test is performed in a 96 wells blank microplate including a filtering membrane at the bottom of the wells. In the first step, the sample is distributed in duplicate for the 2 isotypes (IgA and

IgG) selected in each well containing respectively the Celiac A microspheres mixture, for the IgA isotype and the Celiac G microspheres mixture for the IgG isotype. If the sample tested contains one or more of the suspected antibodies, this (ese) antibody (ies) will bind to the corresponding antigen(s) on the various categories of microspheres. After incubation, a wash step through a filtration process will eliminate the unbound antibodies.

A specific conjugate consisting of either anti-human IgA or IgG antibodies coupled to phycoerythrin, is added to the mixture. It will bind to the previously captured antibodies.

The reaction is then directly measured by the flow cytometer, which categorizes each microspheres set according to its fluorescence color the microspheres while simultaneously measuring the average fluorescence emitted by the conjugate. A calibration system allows expressing by interpolation the titer of the sample for each antigenic specificity.

K. PERFORMANCE CHARACTERISTICS:

1. Analytical performance:

1.1 Precision/Reproducibility:

To evaluate both intra-assay and inter-assay reproducibility, patient sera were analyzed on the FIDIS™ Celiac. These samples were selected to include low, moderate and high positives for each analyte.

Results of the low, moderate and high positive samples are summarized below.

	Within-run (10 tests in the same run)		**Between-run** (5 tests in 5 different runs)	
Antibody specifcity	**Mean value**	**CV (%)**	**Mean value**	**CV (%)**
tTG IgA	41	3.9	42	3.7
tTG IgA	151	4.6	152	5.3
tTG IgA	318	4.0	323	7.0
Glia IgA	41	3.4	42	2.8
Glia IgA	71	2.3	72	2.4
Glia IgA	474	5.5	493	3.1
Glia IgG	69	2.3	70	5.6
Glia IgG	99	4.4	101	7.2
Glia IgG	151	3.5	155	4.6

1.2 Linearity:

Autoantibodies should not be measured in terms of their concentration in serum but as an estimation of the binding capacity between antibody and antigen. This capacity varies between samples and even within the same sample. The main variables characterising these antibodies are the nature of the target epitopes and the quantity of antibodies recognising each of these epitopes. For these reasons, the average binding capacity is the best compromise to represent the mean affinity and avidity of the antibody being studied. The result of this measurement is strongly influenced by the reaction conditions.

FIDIS™ Celiac assay has been optimised to express the average binding capacity at the current dilution (1/200) by a flow cytometric reading resulting of the median fluorescence value obtained from 400 microspheres per parameter.

Further dilutions potentially give rise to inaccurate results because the reaction conditions and the equilibrium of the immunological reaction will be modified

For this reason linearity is sera dependent in all FIDIS tests and there is no dilution effect.

1.3 Traceability (controls, calibrators, or method):

For each assay, a positive control IgA, a positive control IgG and a negative control are included.

1.4 Assay cut-off:

	FIDIS™ Celiac
Negative	<15U/mL for the 3 specificities
Borderline	15-20U/mL for the 3 specificities
Positive	>20U/mL for the 3 specificities

2. Comparison studies:

2.1 Comparison with predicate devices:

The method comparison with predicate devices was performed on 182 samples:

- 66 samples related to Celiac Disease
- 55 samples from blood donors
- 61 samples selected from their potential biological interferences (cryoglobulinemia, hypergammaglobulinemia, IgG and IgM monoclonal immunoglobulins, complement, rheumatoïd factor, hemolyzed sera, plasma and lipemic serum).

Gliadin IgA

		Bindazyme™	
		+	-
FIDIS™	+	55	2
	-	16	109

There were 9 borderline results with the assay. For purposes of calculation, these results were considered as negative.

Positive percent agreement: 77.5% (55/71)
Negative percent agreement: 98.2% (109/111)
Overall agreement: 90.1% (164/182)

tTG IgA

		Bindazyme™	
		+	-
FIDIS™	+	44	0
	-	3	135

There were 7 borderline results with the assay. For purposes of calculation, these results were considered as negative.

Positive percent agreement: 94.0% (44/47)
Negative percent agreement: 100% (135/135)
Overall agreement: 98.3% (179/182)

Gliadin IgG

		Bindazyme™	
		+	-
FIDIS™	+	54	0
	-	6	122

There were 8 borderline results with the assay. For purposes of calculation, these results were considered as negative.

Positive percent agreement: 90% (54/60)
Negative percent agreement: 100% (122/122)
Overall agreement: 96.7% (176/182)

Summary of results

All samples (n=182)	Positive percent agreement	Negative percent agreement	Overall agreement
Gliadin IgA	77.5%	98.2%	90.1%
tTG IgA	94.0%	100%	98.3%
Gliadin IgG	90%	100%	96.7%

2.2 Matrix comparison:

FIDIS™ Celiac and predicate devices use serum.

3. Clinical studies:

The clinical investigation of FIDIS™ Celiac in comparison with Bindazyme™ was studied on the same samples previously tested for the comparative study. Results are compiled below.

a. Clinical sensitivity: *not applicable*

b. Clinical specificity:

The clinical specificity of FIDIS™ Celiac in comparison with Bindazyme™ was studied on the same samples populations previously tested for the comparative study. Results are compiled below.

Blood donors and biological interferences n=116	**ELISA Bindazyme™**			**FIDIS™ Celiac**		
	Pos	Neg	Clinical specificity	Pos	Neg	Clinical specificity
Gliadin IgG	7	109	94%	3	113	97%
Gliadin IgA	22	94	81%	10	106	91%
tTG IgA	1	115	99%	1	115	99%

4. Threshold values and normal range values:

They were estimated from the 2 populations previously used for the comparative study:

- 55 samples from blood donors
- 61 samples selected from their potential biological interferences.

The number of positive samples and the percentage of negative samples by FIDIS™ Celiac is given by the above table.

The negative threshold (<15 U/mL) corresponds to the 97% (113/116) percentile for Gliadin IgG; 91% (106/116) percentile for Gliadin IgA; and 99% (115/116) for tTG IgA for the populations studied.

L. CONCLUSION:

The results of the comparative study show the substantial equivalence of FIDIS™ Celiac to the predicate Bindazyme™ ELISA devices from the Binding Site, Ltd.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

SEP 2 4 2004

Dr. Pascale Laroche
Vice President, Research and Development
Biomedical Diagnostics
Actipole 25 bd de Beaubourg-BP 103
Marne la Vallee, Cedex 2,
France 77423

Re: k041002
Trade/Device Name: FIDIS™ Celiac
Regulation Number: 21 CFR 866.5660
Regulation Name: Multiple autoantibodies immunological test system
Regulatory Class: Class II
Product Code: MVM, MST
Dated: August 5, 2004
Received: August 9, 2004

Dear Dr. Laroche:

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). You may obtain other general information on your responsibilities under the Act 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,

Robert L. Becker, Jr., M.D., Ph.D.
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indications for Use Statement

510(k) Number : K041002

Device Name: FIDIS™ Celiac

Indications for use:

The **FIDIS™ Celiac** kit is a semi-quantitative homogeneous fluorescent-based microparticles immunoassay using flow cytometry readings.
Celiac IgA is designed for the simultaneous detection of human IgA isotype antibodies directed against Gliadin and Tissue Transglutaminase Enzyme.
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The presence of these antibodies can be used in conjunction with clinical findings to aid in the diagnosis of Celiac disease.

The **FIDIS™ Celiac** kit is to be used on serum only.

FIDIS™ Celiac kits are to be used on **FIDIS™ Analyser, software and washer.**

For in vitro diagnostic use.

Prescription Use: X AND/OR Over-The-Counter use: ———
(Part 21 CFR 801 Subpart D) (21 CFR 807 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Maria Chan
Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

510(k) K041002