

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

A. 510(k) Number:

k053012

B. Purpose for Submission:

New Device

C. Measurand:

Anti-Myeloperoxidase antibodies (MPO)

Anti-Serine Proteinase 3 antibodies (PR3)

Anti-Glomerular Basement Membrane antibodies (GBM)

D. Type of Test:

Semi-quantitative

E. Applicant:

Biomedical Diagnostics S.A. (bmd)

F. Proprietary and Established Names:

FIDIS™ VASCULITIS

G. Regulatory Information:

1. Regulation section:

21 CFR 866.5660, Multiple autoantibodies immunological test system

2. Classification:

II

3. Product codes:

MOB, Test system, antineutrophil cytoplasmic antibodies (ANCA)

MVJ, Devices, Measure, Antibodies to Glomerular Basement Membrane (GBM)

4. Panel:

Immunology 82

H. Intended Use:

1. Intended use(s):

The FIDIS™ VASCULITIS* test is a semi-quantitative homogenous fluorescent-based microparticles immunoassay using flow cytometry readings. The test system is used to detect in patient serum samples the presence of anti-neutrophil cytoplasm antibodies (ANCA) directed against Myeloperoxidase (*MPO*) and Serine Proteinase 3 (*PR3*); and anti-glomerular basement membrane (GBM) antibodies. The results of the FIDIS™ VASCULITIS* test are to be used in conjunction with the clinical findings and other laboratory tests to aid in the diagnosis of various primary systemic small vessel vasculitis. The presence of anti-MPO and anti-PR3 antibodies is associated with primary systemic small vessel vasculitis: Wegener's granulomatosis, Churg Strauss syndromes, microscopic periarteritis and idiopathic crescentic glomerulonephritis; and the presence of anti-GBM antibodies is associated with Goodpasture's syndrome.

FIDIS™ VASCULITIS* kit is to be used on the FIDIS Analyser, MLX-BOOSTER Software and Washer. FIDIS™ VASCULITIS* kit could be used with the CARIS™ system (diluting and dispensing device). This test is for in vitro diagnostic use.

*Detection of the serologic markers for primary systemic small vessel vasculitis (ANCA) and for Goodpasture's syndrome (GBM).

2. Indication(s) for use:

Same as intended use

3. Special conditions for use statement(s):
The device is for prescription use only.
4. Special instrument requirements:
FIDIS™ 100 Analyzer (Luminex 100™)
FIDIS™ MLX-Booster Software (k050286)
FIDIS™ Washer (k041002)
Ultrasonic bath

I. Device Description:

Each device contains the following: distinct uniform size color-coded microspheres (each microsphere set is covalently coupled to one of the following antigens: MPO, PR3, and GBM) (ready to use); calibrator (ready to use); positive control (to be diluted); negative control (to be diluted); goat anti-human IgG coupled to phycoerythrin (ready to use); concentrated PBS-Tween (to be diluted with distilled water); one 96 wells microplate including a filtering membrane and a lid.

J. Substantial Equivalence Information:

1. Predicate device name(s):
QuantaLite™ MPO
QuantaLite™ PR3
QuantaLite™ GBM
2. Predicate 510(k) number(s):
k981330 (MPO)
k981328 (PR3)
k984336 (GBM)
3. Comparison with predicate:

Similarities		
Item	New Device	Predicate Device
	FIDIS™ VASCULITIS	Individual INOVA ELISA Assays for autoantibodies to MPO, PR3, and GBM
Intended use	Individual determination of IgG antibodies to MPO, PR3, GBM	Same
Antigen	Purified MPO, PR3, GBM	Same
Sample type	Serum	Same
Type of test	Semi-quantitative	Same
Platform	96 well plates	Same

Differences		
Item	Device	Predicate
Technology	Flow Cytometry	ELISA
Assay Format	Multiplexed	Individual analytes
Sample dilution	1:200	1:101
Substrate	None	TMB
Enzyme-Conjugate	Phycoerythrin	HRP
Detection method	Fluorescence	Colorimetric

Differences		
Item	Device	Predicate
Solid surface (antigen coated)	Color-coded microspheres	Microwells
Instrument	Luminometer (Luminex 100™)	Spectrophotometer
Result Interpretation for each specificity: Anti-MPO, Anti-PR-3, Anti-GBM Antibody	Negative: < 20 AU/mL Equivocal: 20-25 AU/mL Positive: >25 AU/mL	Negative: ≤ 20 Units Weak Pos: 21-30 Units Positive: > 30 units

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

None provided.

L. Test Principle:

FIDIS™ VASCULITIS is a multiplexed semi-quantitative, fluorescent immunoassay performed on the FIDIS™ Analyzer (Luminex 100™) with the MLX Booster software. Each antigen (MPO, PR3, and GBM) is covalently coupled to an individual set of microspheres through its surface functional groups. The different sets of antigen-coupled microspheres are mixed together to constitute the final microspheres reagent and put into wells of a microtiter plate. Prediluted controls and diluted patient sera are added to separate wells allowing autoantibodies to bind to the immobilized antigens on the beads. After incubation, a wash step through a filtration process will remove the unbound antibodies. Then a phycoerythrin labeled anti-human IgG is added to each well and binds to patient autoantibodies/antigen complexes on the microspheres. The samples are subsequently measured in the FIDIS™ Analyzer (flow cytometer) which discriminates the different bead sets as well as measures the fluorescent intensity of the conjugate on each bead. For each sample, the antibody titer for each antigenic specificity is interpolated against a calibration system.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Three samples (weak, moderate and high titers) were analyzed 10 times (for each specificity) in one run for the intra-assay study. The same three samples were analyzed 4 times in 6 different runs for the inter-assay study. The intra-assay CV ranges on Anti-MPO, Anti-PR3, and Anti-GBM were: 1.7% to 5.3%; 2.8% to 10.9%; and 3.8% to 5.7% respectively. The inter-assay CV ranges on Anti-MPO, Anti-PR3, and Anti-GBM were: 6.3% to 8.1%; 10.1% to 13.7%; and 7.1% to 9.1% respectively.

In addition to the above studies, three samples with antibody concentrations close to the cut-off were assayed 10 times in the same run and had %CV of 4.5% to 9.5%; 4.2% to 6.6%; and 3.0 to 12.7% for Anti-MPO, Anti-PR3 and Anti-GBM respectively. For inter-assay reproducibility, three samples close to the cut-off were assayed 4 times in six different runs, had CV of 10.1% to 16.0%, 5.6% to 13.1%, and 4.3% to 11.4% for Anti-MPO, Anti-PR3 and Anti-GBM respectively (see table below).

Antigen	Within-run (Tested 10X in the same run)		Between-run (Tested 4X in 6 different runs)	
	Mean value	CV (%)	Mean value	CV (%)
MPO	28.1	9.5	29.7	10.1
	30.7	7.4	32.0	16.0
	34.7	4.5	33.2	11.3
	42	1.7	39	6.3
	171	5.3	162	8.1
	546	4.0	507	7.4
PR3	29	5.4	27	13.7
	29.1	6.6	28.4	10.3
	41.3	4.2	45.5	5.6
	101	2.8	89	11.0
	178.5	5.8	175.1	13.1
	688	10.9	652	10.1
GBM	30.6	3.0	31.5	4.3
	32.8	12.7	36.5	11.4
	46.3	7.5	53.9	9.3
	49	3.8	45	9.1
	113	2.7	106	6.3
	204	5.7	190	7.1

The reproducibility performance of FIDIS™ VASCULITIS with the CARIS system (diluting and dispensing device) was determined as follows: For the intra-assay study, three samples were analyzed 10 times in one run for each specificity. The same 3 samples were analyzed 4 times in 6 different runs for the inter-assay study. The intra-assay CV ranges on Anti-MPO, Anti-PR3, and Anti-GBM were: 6.3% to 8.8%; 4.7% to 7.0%; and 4.1% to 4.1% respectively. The inter-assay CV ranges on Anti-MPO, Anti-PR3, and Anti-GBM were: 9.1% to 11.8%; 3.9% to 7.0%; and 4.3% to 4.8% respectively (see table below).

Antigen	Within-run (tested 10X in same run)		Between-run (tested 4X in 6 different runs)	
	Mean value	CV (%)	Mean value	CV (%)
MPO	49.5	6.3	43.8	9.1
	54.6	8.8	64.9	11.8
PR3	26.6	7.0	33.1	7.9

	Within-run (tested 10X in same run)		Between-run (tested 4X in 6 different runs)	
	203.1	4.7	204.7	3.9
GBM	46.7	4.1	48.6	4.3
	61.9	4.1	62.8	4.8

Lot to lot reproducibility:

Two lots were analyzed for reproducibility using 3 positive samples (2 near cut off) and 9 negative samples. The acceptable criterion is 25%. The lowest variability was 2% and highest variability was 15%. Both lots were within the 25% variability.

b. Linearity/assay reportable range:

Linearity is not claimed in this assay.

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

There are no reference standard for anti-MPO, anti-PR3 and anti-GBM. The calibrators and controls (positive and negative) were prepared in-house and assigned arbitrary units/mL (AU/mL) during the development process.

d. Detection limit:

Not applicable.

e. Analytical specificity:

Interference study: Twenty eight samples were selected for evaluation of potential interference and crossreactivity: 3 Cryoglobulinemia, 8 Complement, 2 IgG monoclonal immunoglobulins, 3 IgM monoclonal immunoglobulins, 7 Rheumatoid Factor, 3 citrated plasma, and 2 hemolyzed samples. Twenty seven samples were negative and one RF sample was positive for PR3 (see table below). The package insert states to avoid hemolytic, lipemic, icteric samples or samples with abnormal concentration of IgG and/or complement levels or samples with rheumatoid factor.

f. Assay cut-off:

The cut-off value of >25 AU/mL was based on testing 65 samples: 37 normal blood donor sera and 28 selected samples with potential biologic interferences. With this cut-off value, 37 normal donor and 28 selected samples (100%) were negative for MPO and GBM; and 37 normal donor and 27 selected samples (98.5%) were negative for PR3.

2. Comparison studies:

a. Method comparison with predicate device:

Testing was performed on 182 samples: 117 positive for one or more ANCA parameters or positive for GBM; and 65 negative samples. No information about age, gender, and clinical diagnosis was available. Equivocal results were considered negative. The positive, negative and total percent agreements for Anti-MPO, Anti-PR3, and Anti-GBM were shown in tables below.

Anti-MPO		QuantaLite™ MPO		
		Positive	Negative	Total
FIDIST™ VASCULITIS MPO	Positive	31	3	34
	Negative	2	146	148
	Total	33	149	182

Positive percent agreement: 93.9 % (31/33) (95% CI: 85.8% to 100%)

Negative percent agreement: 98% (146/149) (95% CI: 95.7% to 100%)
 Overall percent Agreement: 97.3% (177/182) (95% CI: 94.9% to 99.6%)

Anti-PR3		QuantaLite™ PR3		
		Positive	Negative	Total
FIDIS™ VASCULITIS PR3	Positive	40	3	43
	Negative	7	132	139
	Total	47	135	182

Positive percent agreement: 85.1% (40/47) (95% CI: 74.9% to 95.3%)
 Negative percent agreement: 97.8% (132/135) (95% CI: 95.3% to 100%)
 Overall percent Agreement: 94.5% (172/182) (95% CI: 91.2% to 97.8%)

Anti-GBM		QuantaLite™ GBM		
		Positive	Negative	Total
FIDIS™ VASCULITIS GBM	Positive	21	0	21
	Negative	0	161	161
	Total	21	161	182

Positive percent agreement: 100% (21/21)
 Negative percent agreement: 100% (161/161)
 Overall percent Agreement: 100% (182/182)

Comparison of manual preparation and the automated CARIS™ System:
 Results of the comparison studies are summarized below.

Anti-MPO		Manual FIDIS	
		Positive	Negative
CARIS™ FIDIS	Positive	5	0
	Negative	0	26

Positive percent agreement: 100% (5/5)
 Negative percent agreement: 100% (26/26)
 Overall agreement: 100% (31/31)

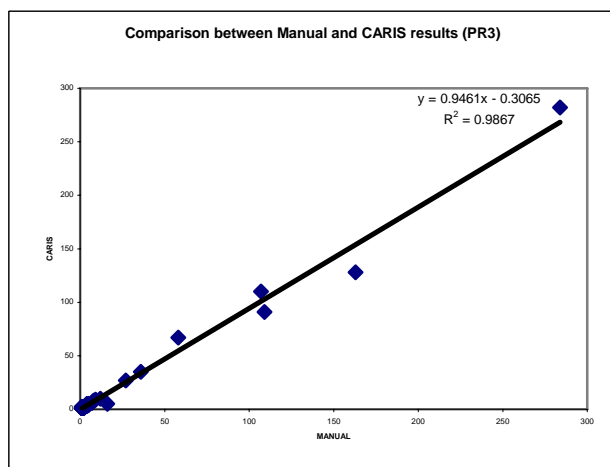
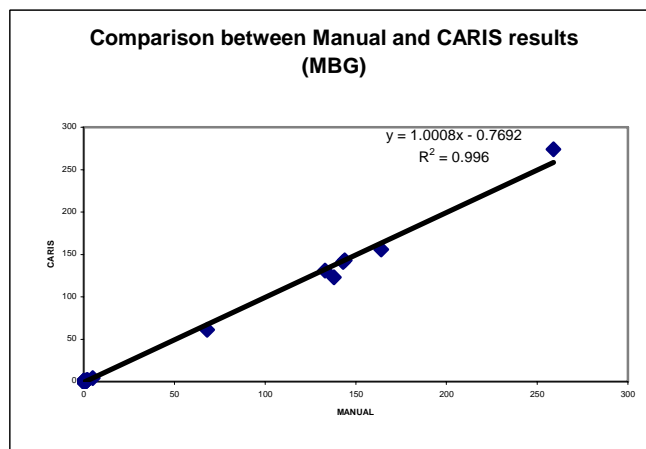
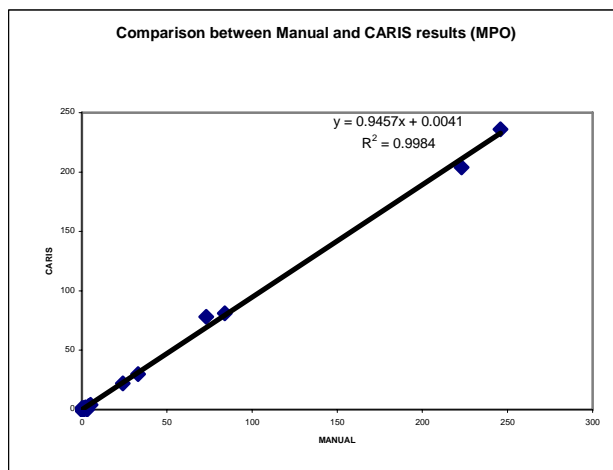
Anti-PR3		Manual FIDIS	
		Positive	Negative
CARIS™ FIDIS	Positive	7	0
	Negative	0	24

Positive percent agreement: 100% (7/7)
 Negative percent agreement: 100% (24/24)
 Overall agreement: 100% (31/31)

Anti-GBM		Manual FIDIS	
		Positive	Negative
CARIS™ FIDIS	Positive	7	0
	Negative	0	24

Positive percent agreement: 100% (7/7)
 Negative percent agreement: 100% (24/24)
 Overall agreement: 100% (31/31)

Linear Regression analysis of antigenic specificities with CARIS™.



b. Matrix comparison:

Serum is the only recommended matrix.

3. Clinical studies:

- a. *Clinical sensitivity and specificity:*
Not applicable.
- b. *Other clinical supportive data (when a. is not applicable):*
Not applicable.
4. Clinical cut-off:
Same as assay cut-off.
5. Expected values/Reference range:
Expected values in the normal population should be negative.

Table of incidence on Diseases with PR3, MPO and GBM antibodies

Diseases	PR3	MPO	GBM	Reference
Wegener's granulomatosis	30-90%			14
	50-90%			15
Churg Strauss Syndrome	35%	35%		14
	31%	7%		15
Microscopic periarthritis	20-40%	50%		14
	25-30%	36%		15
Idiopathic glomerulonephritis	20-40%	50%		14
		80%		15
Goodpasture's syndrome or anti- GBM nephritis			98%	16

(14) MOLLOY P. ANCA and Associated disease: Update. PSA Consult, 2000, vol III, 5.

(15) SANCHEZ-LALLOYER N. Anti-neutrophil cytoplasmic antibodies. Spectra Biologie, 1993; 93/3: 38-42.

(16) ROSSERT J. Goodpasture's disease. Orphanet encyclopedia, 2002: 1-4.

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.