

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

A. 510(k) Number:

k070458

B. Purpose for Submission:

New device

C. Measurand:

Anti-Myeloperoxidase Antibodies (MPO)

Anti-Serine Protease 3 Antibodies (PR3)

Anti-Glomerular Membrane Antibodies (GBM)

D. Type of Test:

Semi-quantitative

E. Applicant:

Biomedical Diagnostics, S.A. (bmd)

F. Proprietary and Established Names:

FIDIS™ VASCULITIS, MX 007

G. Regulatory Information:

1. Regulation section:

21 CFR § 866.5660, Multiple autoantibodies, immunological test system

2. Classification:

Class II

3. Product codes:

MOB, Test System, antineutrophil 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* kit is a semi-quantitative homogeneous 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 the other laboratory tests to aid in the diagnosis of various primary systemic small vessel vasculitis.

The presence of anti-MPO and anti-PR3 antibodies associated 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 used on the FIDIS Analyser, MLX-BOOSTER Software and FIDIS™ Washer.

FIDIS™ VASCULITIS* kit could be used with 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 syndrome (GBM)*

2. Indication(s) for use:
Same as Intended use.
3. Special conditions for use statement(s):
For prescription only.
4. Special instrument requirements:
FIDIS™ 100 or FIDIS™ 200 Analyzer (Luminex 100™ or 200™)
FIDIS™ MLX-007 Software
FIDIS™ XY Platform
FIDIS™ Sheath Delivery System (SD)
Computer Central Processing Unit (PC)
Computer Monitor Screen
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); sample dilution buffer (ready to use); wash buffer PBS-Tween (ready to use); one 96 wells microplate including a filtering membrane and a lid.

J. Substantial Equivalence Information:

1. Predicate device name(s):
FIDIS™ VASCULITIS
2. Predicate K number(s):
k053012
3. Comparison with predicate:

Similarities		
Item	New Device	Predicate Device
	FIDIS™ VASCULITIS (MX 007)	FIDIS™ VASCULITIS
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
Technology	Flow Cytometry	Same
Assay Format	Multiplexed	Same

Similarities		
Item	New Device	Predicate Device
Sample dilution	1:200	Same
Substrate	None	Same
Enzyme-Conjugate	Phycoerythrin	Same
Detection method	Fluorescence	Same
Solid surface (antigen coated)	Color-coded microspheres	Same
Result Interpretation for each specificity: Anti-MPO, Anti-PR-3, Anti-GBM Antibody	Negative: < 20 AU/mL Borderline: 20-25 AU/mL Positive: >25 AU/mL	Same

Differences		
Item	Device	Predicate
Instrument	Luminometer (Luminex 100™ and/or Luminex 200™)	Luminometer (Luminex 100™)
Calibrator	2 Wells/Test	1 Well/Test
Software version	MLX Booster version 2.2	MLX Booster version 1.35

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

None provided.

L. Test Principle:

FIDIS™ VASCULITIS is based on the use of distinct uniform size color-coded microspheres and a bench top flow cytometer interfaced to digital signal processing hardware and software. A red diode laser beam in the flow cytometer classifies each set of microspheres on the basis of its unique fluorescence intensity (red to orange) thus identifying which analyte is being tested. At the same time, a green laser beam illuminates the external second molecule fluorescence to quantify the reaction related to the specific 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, constituting the final microspheres reagent.

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 each well containing the microspheres mixture. If this sample contains one or more of the suspected antibodies, this(ese) antibody(ies) bind to the corresponding antigen(s) on the various sets of microspheres.
- After incubation, the unbound antibodies are removed by a wash step using a filtration process.

- A phycoerythrin labeled anti-human IgG conjugate is then added that binds to the previously bound antibodies.
- A final wash step stops the reaction.
- The reaction is then directly measured by the flow cytometer, which differentiates each set of microspheres according to its fluorescence color while simultaneously measures the average fluorescence emitted by the conjugate.

A calibration system permits the determination of the antibody titer of each sample by interpolation for each antigenic specificity.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
 - a. *Precision/Reproducibility:*

For the intra-assay study, six samples for MPO, six samples for PR3, seven samples for GBM (weak, moderate and high titers) were analyzed 10 times (for each specificity) in one run. For the inter-assay study, the same samples were analyzed 3 times in 5 different runs. The intra-assay CV ranges for Anti-MPO, Anti-PR3, and Anti-GBM were: 4.9% to 12.4%; 3.3% to 11.6%; and 2.3% to 11.3% respectively. The inter-assay CV ranges on Anti-MPO, Anti-PR3, and Anti-GBM were: 5.4% to 11.2%; 10.9% to 19.6%; and 3.8% to 14.6% respectively (see table below).

Antigen	Sample #	Within-run		Between-run	
		Mean value	CV (%)	Mean value	CV (%)
MPO	1	15	5.3	18	11.2
	2	28	7.5	28	6.2
	3	33	12.4	35	10.9
	4	54	8.0	56	10.5
	5	261	10.8	261	10.1
	6	391	4.9	392	5.4
PR3	7	16	11.3	20	19.6
	8	30	9.7	31	12.0
	9	37	11.6	43	14.2
	10	73	3.3	76	10.9
	11	198	6.1	222	13.8
	12	266	7.2	303	13.4
GBM	13	10	11.3	11	14.6
	14	36	10.6	38	12.0
	15	40	5.8	46	6.8
	16	59	2.3	60	6.1
	17	120	7.3	122	6.9
	18	215	5.6	215	5.7
	19	321	2.7	326	3.8

The reproducibility performance of FIDIS™ VASCULITIS with the CARIS system (diluting and dispensing device) was determined as follows: Six samples for MPO, seven samples for PR3, six samples for GBM were analyzed 10 times in one run (on each specificity) for the intra-assay study.

The same samples were analyzed 3 times in 5 different runs for the inter-assay study. The intra-assay CV ranges on Anti-MPO, Anti-PR3, and Anti-GBM were: 2.6% to 10.8%; 3.8% to 7.2%; and 3.8% to 7.1% respectively. The inter-assay CV ranges on Anti-MPO, Anti-PR3, and Anti-GBM were: 6.7% to 13.6; 5.9% to 11.7%; and 5.9 to 9.7% respectively (see table below).

Antigen	Sample #	Within-run		Between-run	
		Mean value	CV (%)	Mean value	CV (%)
MPO	1	17	6.4	17	13.6
	2	21	4.9	22	6.7
	3	29	3.8	30	7.6
	4	37	4.3	38	8.4
	5	59	2.6	57	9.3
	6	94	10.8	96	9.4
PR3	7	16	6.9	16	6.9
	8	21	5.0	20	7.8
	9	24	5.9	24	7.4
	10	36	3.8	34	5.9
	11	63	6.5	60	11.7
	12	83	7.2	80	7.6
	13	386	7.2	371	6.8
GBM	14	13	4.9	12	8.2
	15	42	7.0	42	5.9
	16	55	3.8	53	6.5
	17	90	6.4	87	7.9
	18	115	7.1	117	9.7
	19	392	4.8	400	7.5

Lot to lot reproducibility:

Two lots were analyzed 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 standards for anti-MPO, anti-PR3 and anti-GBM. The calibrators and controls (positive and negative) were prepared in-house and assigned arbitrary units (AU/mL) during the development process.

d. Detection limit:

Not applicable.

e. Analytical specificity:

Interference study: Twenty seven samples were selected for evaluation of potential interference and crossreactivity: 2 Cryoglobulinemia, 8 Complement, 2 IgG monoclonal immunoglobulins, 3 IgM monoclonal immunoglobulins, 7 Rheumatoid Factor, 3 citrated plasmas, and 2 hemolyzed samples. Twenty six samples were negative and one RF sample was positive

for PR3. To ensure appropriate samples are used in the test, the package insert states to avoid grossly hemolyzed, lipemic, microbially contaminated, heat-treated, specimens with visible particulates, 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 consisted of 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 219 samples which included 135 positive for one or more ANCA antibodies and/or positive for GBM; and 84 negative samples. No information about age, gender, and clinical status were available. Equivocal results were considered negative. The positive, negative and total percent agreements for Anti-MPO, Anti-PR3, and Anti-GBM are shown in tables below.

Anti-MPO		FIDIS™ VASCULITIS MPO		
		Positive	Negative	Total
FIDIS™ VASCULITIS (MX 007) MPO	Positive	69	0	69
	Negative	2	148	150
	Total	71	148	219

Positive percent agreement: 97.2 % (69/71)

Negative percent agreement: 100% (148/148)

Overall percent Agreement: 99.1% (217/219)

Anti-PR3		FIDIS™ VASCULITIS PR3		
		Positive	Negative	Total
FIDIS™ VASCULITIS (MX 007) PR3	Positive	47	1	48
	Negative	2	169	171
	Total	49	170	219

Positive percent agreement: 95.9% (47/49)

Negative percent agreement: 99.4% (169/170)

Overall percent Agreement: 98.6% (216/219)

Anti-GBM		FIDIS™ VASCULITIS GBM		
		Positive	Negative	Total
FIDIS™ VASCULITIS (MX 007) GBM	Positive	25	0	25
	Negative	0	194	194
	Total	25	194	219

Positive percent agreement: 100% (25/25)
 Negative percent agreement: 100% (194/194)
 Overall percent Agreement: 100% (219/219)

Comparison of manual preparation and the automated CARIS™ System:
 Testing was performed on 117 samples: 75 positive for one or more ANCA parameters and/or positive for GBM; and 42 negative samples including some samples evaluated for their potential biological interferences. Results are summarized in tables below.

Anti-MPO		Manual FIDIS		
		Positive	Negative	Total
CARIS™ FIDIS	Positive	34	2	36
	Negative	0	81	81
	Total	34	83	117

Positive percent agreement: 100% (34/34)
 Negative percent agreement: 97.6% (81/83)
 Overall agreement: 98.3% (115/117)

Anti-PR3		Manual FIDIS		
		Positive	Negative	Total
CARIS™ FIDIS	Positive	25	2	27
	Negative	0	90	90
	Total	25	92	117

Positive percent agreement: 100% (25/25)
 Negative percent agreement: 97.8% (90/92)
 Overall agreement: 98.3% (115/117)

Anti-GBM		Manual FIDIS		
		Positive	Negative	Total
CARIS™ FIDIS	Positive	23	0	23
	Negative	0	94	94
	Total	23	94	119

Positive percent agreement: 100% (23/23)
 Negative percent agreement: 100% (94/94)
 Overall agreement: 100% (117/117)

- b. Matrix comparison:
 Serum is the only recommended matrix.
- 3. Clinical studies:
 - a. Clinical Sensitivity:
 Not applicable.
 - b. Clinical specificity:
 Not applicable.
 - c. Other clinical supportive data (when a. and b. are 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-Lallyoyer N. ANCA. 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.