June 4, 2018

BUHLMANN Laboratories AG
Roshana Ahmed
Associate Director, Regulatory Affairs
Mapi SRS, an ICON plc Company
2343 Alexandria Drive
Suite 100
Lexington, Kentucky 40504

Re: K181012
Trade/Device Name: BUHLMANN fCAL ELISA
Regulation Number: 21 CFR 866.5180
Regulation Name: Fecal calprotectin immunological test system
Regulatory Class: Class II
Product Code: NXO
Dated: April 16, 2018
Received: April 17, 2018

Dear Roshana Ahmed:

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. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. 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 Part

801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Kelly Oliner -S

For
Lea Carrington, Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K181012

Device Name
BUHLMANN fCAL(R) ELISA

Indications for Use *(Describe)*

The BÜHLMANN fCAL® ELISA is an in vitro diagnostic assay intended for the quantitative measurement of fecal calprotectin in human stool. The BÜHLMANN fCAL® ELISA aids in the diagnosis of inflammatory bowel disease (IBD), specifically Crohn's disease (CD) and ulcerative colitis (UC) and aids in the differentiation of IBD from irritable bowel syndrome (IBS) in conjunction with other laboratory and clinical findings.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

I. Submitter

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Contact Person: Alicja Ritz, Ph.D., Head Regulatory Affairs
Date Prepared: May 22, 2018

II. Device

Device Proprietary Name:	BÜHLMANN fCAL® ELISA
Common or Usual Name:	Fecal calprotectin immunological test system
Classification Name:	Calprotectin, Fecal
Regulation Number:	21 CFR 866.5180
Product Code:	NXO
Device Classification	II

III. Predicate Device

Substantial equivalence is claimed to the following device:

- Calprest®NG, K160447, Eurospital S.p.A.

IV. Device Description

The BÜHLMANN fCAL® ELISA is an enzyme-linked immunosorbent assay (ELISA) performed using patient stool extracts collected without preservatives. Calprotectin within the extract binds to protein specific antibodies coated on the well surface. An enzyme conjugated antibody detects the captured antigen. Incubation of the complex with substrate results in a colored product which reflects the amount of calprotectin in the sample. Quantification of calprotectin concentration is achieved using standard plate readers.

V. Indications for Use

The BÜHLMANN fCAL® ELISA is an in vitro diagnostic assay intended for the quantitative measurement of fecal calprotectin in human stool. The BÜHLMANN fCAL® ELISA aids in the diagnosis of inflammatory bowel disease (IBD), specifically Crohn's disease (CD) and ulcerative colitis (UC) and aids in the differentiation of IBD from irritable bowel syndrome (IBS) in conjunction with other laboratory and clinical findings.

VI. Comparison of Technological Characteristics

The BÜHLMANN fCAL® ELISA and the Calprest®NG share the following characteristics:

- use of ELISA technology to detect calprotectin in stool samples;
- use of quantitative assay format;
- use of 96 well microtiter plate;
- use of TMB as substrate; and
- optical density reading at 450 nm.

The BÜHLMANN fCAL® ELISA is technologically different from the Calprest®NG as follows:

- use of different sample extraction buffers and sample dilution;
- use of different antibodies for microtiter plate coating;
- use of different detection antibodies;
- use of different calibrator concentrations;
- use of a different standardization;
- different clinical thresholds; and
- different reportable ranges.

The tables below compares key technological features between the subject and predicate devices.

Technological comparison

BÜHLMANN fCAL® ELISA Reagents

Similarities		
Parameter	**BÜHLMANN fCAL® ELISA**	**Calprest®NG (K160447)**
Method	Colorimetric ELISA	Colorimetric ELISA
Analyte	Calprotectin	Calprotectin
Assay Format	Quantitative	Quantitative
Sample Type	Fecal	Fecal
Platform	96-well microtiter plate	96-well microtiter plate
Conjugate	HRP Horse Radish Peroxidase	HRP Horse Radish Peroxidase
Substrate	TMB	TMB
OD Reading	450 nm	450 nm

Differences		
Parameter	**BÜHLMANN fCAL® ELISA**	**Calprest®NG (K160447)**
Reportable Range	30 - 1800 µg/g (mg/kg)	27.1 – 3000 mg/kg
Sample Volume	< 1 g	1 – 5 g
Sample Dilution	1:7500	1:20,000
Result interpretation	Normal: < 80 µg/g Gray-zone: 80 - 160 µg/g Elevated: > 160 µg/g	Normal: < 50 mg/kg (µg/g) Borderline: 50 – 120 mg/kg (µg/g) Abnormal: > 120 mg/kg (µg/g)

BÜHLMANN fCAL® ELISA Controls

Parameter	**BÜHLMANN fCAL® ELISA**	**Calprest®NG (K160447)**
Method	BÜHLMANN fCAL® ELISA	Calprest®NG
Analyte	Native human calprotectin	Recombinant calprotectin antigen (rAg)
Levels	2 (high and low)	2 (high and low)
Physio-chemical characteristics	Ready to use	Ready to use

BÜHLMANN fCAL® ELISA Calibrators

Parameter	**BÜHLMANN fCAL® ELISA**	**Calprest®NG (K160447)**
Method	BÜHLMANN fCAL® ELISA	Calprest®NG
Analyte	Native human calprotectin	Recombinant calprotectin antigen (rAg)
Calibrators	5 levels: 4, 12, 40, 120, and 240 ng/mL	6 levels: 0, 2.5, 12.5, 25, 50, and 150 ng/mL
Conversion factor	7.5	20
Nominal Value Assignment	30 µg/g 90 µg/g 300 µg/g 900 µg/g 1800 µg/g	0 50 µg/g 250 µg/g 500 µg/g 1000 µg/g 3000 µg/g

Discussion

As seen above, the differences between the subject and predicate devices include the use of different sample extraction buffers and dilution ratios, use of different antibodies and calibrator concentrations, and use of different cut-offs. These differences are addressed by the performance data identified below.

VII. Summary of Performance Characteristics

The following performance studies were conducted in support of the substantial equivalence determination:

- establishment of clinical thresholds;
- traceability/standardization;
- precision/reproducibility;
- linearity;
- accuracy/recovery;
- interfering substances;
- analytical sensitivity;
- stability (analyte and reagent); and
- clinical study.

A. Clinical Thresholds

Calprotectin Concentration	Interpretation	Follow-Up
< 80 µg/g	Normal	None
80 µg/g ≤ x ≤ 160 µg/g	Gray-zone/Borderline	Retest within 4 – 6 weeks
> 160 µg/g	Elevated	Retest as appropriate

B. Precision

Single-Site Repeatability Study Results

Sample	Mean	n	Within-run (Repeatability)		Between-run		Between-day		Total (Within-Laboratory)	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
P1	38.5	80	2.3	5.8%	1.8	4.8%	2.2	5.6%	3.6	9.4%
P2	67.0	80	2.0	3.0%	3.5	5.2%	1.6	2.4%	4.3	6.4%
P3	135.7	80	2.3	1.7%	5.6	4.1%	0	0%	6.0	4.4%
P4	207.1	80	4.1	2.0%	12.5	6.0%	0	0%	13.2	6.4%
P5	337.1	80	5.9	1.8%	18.3	5.4%	0	0%	19.3	5.7%
P6	562.6	80	11.0	2.0%	13.6	2.4%	2.5	0.4%	17.7	3.1%
P7	918.0	80	18.6	2.0%	62.1	6.8%	20.8	2.3%	68.1	7.4%

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Multi-Site Precision Study Results

Sample	Mean	n	Within-run		Between-run		Between-day		Between-operator		Between-site		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
S01	41.4	240	3.1	7.4%	8.1	19.6%	0.0	0.0%	0.0	0.0%	4.1	9.9%	9.6	23.2%
S02	67.2	240	3.0	4.4%	7.0	10.4%	0.0	0.0%	1.9	2.8%	3.9	5.8%	8.8	13.0%
S03	143.0	240	5.6	3.9%	15.7	11.0%	0.0	0.0%	2.6	1.8%	3.7	2.6%	17.3	12.1%
S04	379.8	240	10.8	2.9%	16.4	4.3%	3.2	0.9%	0.0	0.0%	13.7	3.6%	24.2	6.4%
S05	1056.6	240	40.1	3.8%	53.8	5.1%	0.0	0.0%	39.6	3.7%	67.6	6.4%	103.1	9.8%

Lot-to-Lot Reproducibility Study Results

Sample	Mean (µg/g)	n	Within-run		Between-day		Between-reader		Between-operator		Between-lot		Total	
			SD (µg/g)	%CV	SD (µg/g)	%CV	SD (µg/g)	%CV	SD (µg/g)	%CV	SD (µg/g)	%CV	SD (µg/g)	%CV
2	46.4	74	2.5	5.5%	0.5	1.1%	2.3	5.0%	1.5	3.2%	2.4	5.3%	4.5	9.7%
3	105.5	75	2.5	2.4%	1.4	1.4%	2.6	2.4%	0.8	0.8%	2.1	2.0%	4.5	4.2%
4	133.6	75	5.0	3.8%	1.9	1.4%	2.2	1.7%	0.0	0.0%	4.2	3.2%	7.2	5.4%
5	178.5	75	6.3	3.5%	0.0	0.0%	0.7	0.4%	2.3	1.3%	6.3	3.5%	9.2	5.2%
6	435.2	75	12.4	2.9%	7.5	1.7%	0.0	0.0%	0.0	0.0%	18.1	4.2%	23.2	5.3%
7	1476.1	75	48.4	3.3%	88.6	6.0%	0.0	0.0%	32.2	2.2%	31.4	2.1%	110.6	7.5%

Extraction Reproducibility Study Results

Sample	Mean (µg/g)	n	Within-extraction		Between-extraction		Total	
			SD (µg/g)	%CV	SD (µg/g)	%CV	SD (µg/g)	%CV
S01	51.2	20	4.5	8.9%	7.8	15.2%	9.0	17.6%
S03	88.3	20	6.6	7.5%	13.3	15.0%	14.8	16.8%
S05	66.8	20	10.6	15.8%	3.7	5.5%	11.2	16.7%
S06	179.3	20	16.8	9.4%	32.8	18.3%	36.8	20.5%
S07	366.1	20	22.4	6.1%	32.3	8.8%	39.3	10.7%
S08	327.4	20	15.4	4.7%	26.9	8.2%	31.0	9.5%
S09	1783.7	20	198.3	11.1%	262.0	14.7%	328.6	18.4%

C. Linearity

Analytical measuring range: 30 – 1800 µg/g.

D. Accuracy/Recovery

Specimen Extract	Mean Baseline Result (µg/g)	Expected Post-Spike Result (µg/g)	Observed Post-Spike Result (µg/g)	Recovery rate (%)
#1	46.5	226.5	224.5	99.1%
#2	63.7	243.7	247.7	101.6%
#3	89.0	269.0	274.9	102.2%
#4	111.6	291.6	292.0	100.1%
#5	163.5	343.5	331.1	96.4%
#6	304.0	484.0	475.0	98.1%
#7	990.2	1170.2	1166.6	99.7%

E. Analytical Sensitivity

LoB = 8.3 µg/g (mg/kg)
LoD = 12.6 µg/g (mg/kg)
LoQ = 30 µg/g (mg/kg)

F. Interfering Substances

Study procedures were performed using the following four (4) stool specimen extracts:

- one extract with calprotectin concentration close to the lower measuring limit of 30 µg/g;
- one extract with calprotectin concentration of approximately 100 µg/g;
- one extract with calprotectin concentration of approximately 200 µg/g; and
- one extract with calprotectin concentration of approximately 500 µg/g.

The following analytes, pharmaceuticals and nutritional supplements did not interfere with the BÜHLMANN fCAL® ELISA when added to stool extracts at the given test concentrations:

Trade name	**Active component**	**Solvent**	**Concentration (mg/mL)**
gyno-Tardyferon	Iron (II) sulfate	HCl / NaOH	0.04
Prednisone	Prednisone	DMSO	0.13
Imurek	Azathioprine	DMSO	0.08
Salofalk	Mesalamine; 5-ASA	DMSO	2.09
Agopton	Lansoprazole	Dimethylformamide	0.07
Asacol	Mesalamine; 5-ASA	DMSO	1.00
Vancocin	Vancomycin	H_2Odd	0.80
Sulfamethoxazole	Sulfamethoxazole	DMSO	0.64
Trimethoprim	Trimethoprim lactate	DMSO / Exbuffer	0.14
Ciproxine	Ciprofloxacin	solvent from manufacturer / H_2Odd	0.50
Vitamin E	DL-α Tocopherol Acetate	H_2O+Tween	0.12
Bion 3	Multivitamin	HCl / NaOH	0.43
Hemoglobin	Hemoglobin	H_2Odd	0.50

The following microorganisms did not interfere with the BÜHLMANN fCAL® ELISA when added to stool extracts at the given cell counts:

Microorganism	**Concentration (cfu/mL)**
Escherichia coli	9.5×10^7
Salmonella enterica subsp. enterica	1×10^9
Klebsiella pneumoniae subsp. pneumonia	5.4×10^7
Citrobacter freundii	9.7×10^7
Shigella flexneri	1.5×10^8
Yersinia enterocolitica subsp. enterocolitica	1.6×10^8

G. Clinical Study (Clinical Sensitivity/Specificity of IBD vs. non-IBD)

Borderline Values considered Positive		**IBD**		**Total**
		Positive	**Negative**	
BÜHLMANN fCAL® ELISA	**Positive**	126	60	186
	Negative	9	142	151
	Total	135	202	337
Sensitivity = 93.3%; 95% C.I. (87.7%, 96.9%)				
Specificity = 70.3%; 95% C.I. (63.5%, 76.5%)				
PPV = 67.7%; 95% C.I. (60.5%, 74.4%)				
NPV = 94.0%; 95% C.I. (89.0%, 97.2%)				

Borderline Values considered Negative		**IBD**		**Total**
		Positive	**Negative**	
BÜHLMANN fCAL® ELISA	**Positive**	114	33	147
	Negative	21	169	190
	Total	135	202	337
Sensitivity = 84.4%; 95% C.I. (77.2%, 90.1%)				
Specificity = 83.7%; 95% C.I. (77.8%, 88.5%)				
PPV = 77.6%; 95% C.I. (69.9%, 84.0%)				
NPV = 88.9%; 95% C.I. (83.6%, 93.0%)				

H. Clinical Study (Clinical Sensitivity/Specificity of IBD vs. IBS)

Borderline Values considered Positive		**Clinical Diagnosis**		**Total**
		IBD	**IBS**	
BÜHLMANN fCAL® ELISA	**Positive**	126	36	162
	Negative	9	94	103
	Total	135	130	265
Sensitivity = 93.3%; 95% C.I. (87.7%, 96.9%)				
Specificity = 72.3%; 95% C.I. (63.8%, 79.8%)				
PPV = 77.8%; 95% C.I. (70.6%, 83.9%)				
NPV = 91.3%; 95% C.I. (84.1%, 95.9%)				

Borderline Values considered Negative		**Clinical Diagnosis**		**Total**
		IBD	**IBS**	
BÜHLMANN fCAL® ELISA	**Positive**	114	19	133
	Negative	21	111	132
	Total	135	130	265
Sensitivity = 84.4%; 95% C.I. (77.2%, 90.1%)				
Specificity = 85.4%; 95% C.I. (78.1%, 91.0%)				
PPV = 85.7%; 95% C.I. (78.6%, 91.2%)				
NPV = 84.1%; 95% C.I. (76.7%, 89.9%)				

VIII. Conclusion

The information provided above supports that the BÜHLMANN fCAL® ELISA is as safe and effective as the predicate devices. Although technological differences exist between the subject and predicate devices, performance testing supports that these differences do not raise any new questions of safety and effectiveness. Therefore, it is concluded that the BÜHLMANN fCAL® ELISA is substantially equivalent to the predicate devices.

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