510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K181012

B. Purpose for Submission:

New Device

C. Measurand:

Fecal calprotectin

D. Type of Test:

Quantitative, ELISA

E. Applicant:

BÜHLMANN Laboratories AG

F. Proprietary and Established Names:

BÜHLMANN fCAL ELISA

G. Regulatory Information:

1. Regulatory Section:

   21 CFR 866.5180, Fecal calprotectin immunological test system

2. Classification:

   Class II

3. Product Code:

   NXO, Calprotectin, Fecal

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended 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.

2. Indication for use:

   Same as Intended Use

3. Special conditions for use statement:

   Prescription use only

4. Special instrument requirements:

   Microtiter plate reader (450 nm filter)

I. Device Description:

The BÜHLMANN fCAL ELISA kit contains the following materials for EK-CAL (96 tests):

- Extraction Buffer (125 mL each, 3 bottles)
- Incubation Buffer (125 mL each, 2 bottles)
- Microplate coated with anti-calprotectin monoclonal antibody (12 x 8-well strip)
- Plate Sealer (3 pieces)
- 10x Wash buffer concentrate (100 mL, 1 bottle)
- Enzyme Label Anti-calprotectin monoclonal antibody conjugated to horseradish peroxidase (12 mL, 1 vial)
- Tetramethylbenzidine (TMB) substrate (12 mL, 1 vial)
- Stop Solution, 0.25 M sulfuric acid (12 mL, 1 vial)
- Calibrators A–E: Human serum calprotectin in a buffer matrix (1 mL each, 5 vials)
- Control Low/High: Human serum calprotectin in a buffer matrix (1 mL each, 2 vials)

J. Substantial Equivalence Information:

1. Predicate device name:

   Calprest NG

2. Predicate 510(k) number:

   K160447

3. Comparison with predicate:

Similarities		
Item	**BÜHLMANN fCAL ELISA**	**Calprest NG**
Intended 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.	Calprest NG is a quantitative ELISA for detecting concentration of fecal calprotectin, which can be used as an in vitro diagnostic to aid in the diagnosis of Inflammatory Bowel Diseases (IBD), specifically Crohn's disease and ulcerative colitis, and to differentiate IBD from Irritable Bowel Syndrome (IBS) in conjunction with other clinical and laboratory findings.
Method	Colorimetric ELISA	Same
Analyte	Calprotectin	Same
Assay Format	Quantitative	Same
Sample Type	Fecal	Same
Platform	96-well microtiter plate	Same
Conjugate	Horse Radish Peroxidase (HRP)	Same
Substrate	Tetramethylbenzidine (TMB)	Same
OD Reading	450 nm	Same

Differences		
Item	**BÜHLMANN fCAL ELISA**	**Calprest NG**
Reportable Range	30–1,800 µg/g	27.1–3,000 µg/g
Specimen Requirement	< 1 g	1–5 g
Sample Dilution	1:7,500	1:20,000
Result interpretation	Normal: < 80 µg/g Gray-zone: 80–160 µg/g Elevated: > 160 µg/g	Normal: < 50µg/g Borderline: 50–120 µg/g Abnormal: > 120 µg/g
Controls	2 levels: Native human calprotectin	2 levels: Recombinant calprotectin antigen
Calibrators	5 levels: 30, 90, 300, 900, and 1,800 µg/g	6 levels: 0, 50, 250, 500, 1,000, and 3,000 µg/g
Calibrator conversion factor	7.5 Conversion of ng/mL to µg/g calprotectin	20 Conversion of ng/mL to µg/g calprotectin
Extraction Solution	Ready to use	2.5x Concentrate
Sample Buffer Diluent	Ready to use	10x Concentrate
Wash Buffer	10x Concentrate	20x Concentrate

K. Standard/Guidance Documents Referenced:

- CLSI EP5-A3 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition
- CLSI EP6-A Evaluation of The Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
- CLSI EP7-A2 Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition
- CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition
- CLSI EP25-A Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline

- CLSI EP28-A3c Defining, Establishing, And Verifying Reference Intervals in The Clinical Laboratory; Approved Guideline – Third Edition (formerly CLSI C28-A3c)
- CLSI X5-R Metrological Traceability and Its Implementation; A Report

L. Test Principle:

The BÜHLMANN fCAL ELISA is an enzyme-linked immunosorbent assay (ELISA) performed using patient stool samples collected without preservatives and contains a microtiter plate coated with monoclonal antibodies (mAb) for calprotectin. Extracted patient stool samples, calibrators, and controls are incubated in the wells. After the washing step, a monoclonal detection antibody conjugated to horseradish peroxidase (HRP) binds to the calprotectin molecules bound to the antibody coated onto the plate. After incubation and a further washing step, Tetramethylbenzidine (TMB) is added as a substrate (blue color formation) followed by a stopping reaction (change to yellow color). The absorption of calibrators, controls, and samples are measured at 450 nm. The intensity of the color is proportional to the amount of conjugate bound, and thus to the amount of captured calprotectin. The concentration of calprotectin in the extracted sample is interpreted from a standard curve generated from the five calibrators and converted to µg of calprotectin per g of stool using a conversion factor supplied in the package insert. Samples determined to have < 80 µg/g are interpreted as normal, while samples determined to have 80 – 160 µg/g fall into a gray zone that should be repeated within four to six weeks, and samples determined to have > 160 µg/g are interpreted as elevated.

M. Performance Characteristics:

1. Analytical performance: All results presented below met the manufacturer's pre-determined acceptance criteria.

   a. Precision/Reproducibility:

   Precision: Seven extracted stool samples of various concentrations of calprotectin were tested for 10 days with two runs per day in four replicates per run, for a total of 80 fCAL ELISA test results per sample. The mean fCAL ELISA test result was computed and the within-run, between-run, between-day, and total standard deviations (SD) and associated coefficients of variation (%CV) were estimated.

Sample	Mean (µg/g)	Within-Run		Between-Run		Between-Day		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	38.5	2.3	5.8%	1.8	4.8%	2.2	5.6%	3.6	9.4%
2	67.0	2.0	3.0%	3.5	5.2%	1.6	2.4%	4.3	6.4%
3	135.7	2.3	1.7%	5.6	4.1%	0.0	0%	6.0	4.4%
4	207.1	4.1	2.0%	12.5	6.0%	0.0	0%	13.2	6.4%
5	337.1	5.9	1.8%	18.3	5.4%	0.0	0%	19.3	5.7%
6	562.6	11.0	2.0%	13.6	2.4%	2.5	0.4%	17.7	3.1%
7	918.0	18.6	2.0%	62.1	6.8%	20.8	2.3%	68.1	7.4%

Reproducibility: To evaluate between-operator imprecision and between-site reproducibility, five extracted stool samples at various concentrations of calprotectin were tested for five days with two runs per day in four replicates per run at three sites by two operators, allowing for a total of 240 fCAL ELISA test results per sample. The mean fCAL ELISA test result was computed and the within-run, between-run, between-day, between-operator, between-site, and total standard deviations (SD) and associated coefficients of variation (%CV) were calculated.

Sample	Mean (µg/g)	Within-run		Between-run		Between-day		Between-operator		Between-site		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	41.4	3.1	7.4%	8.1	19.6%	0.0	0.0%	0.0	0.0%	4.1	9.9%	9.6	23.2%
2	67.2	3.0	4.4%	7.0	10.4%	0.0	0.0%	1.9	2.8%	3.9	5.8%	8.8	13.0%
3	143.0	5.6	3.9%	15.7	11.0%	0.0	0.0%	2.6	1.8%	3.7	2.6%	17.3	12.1%
4	379.8	10.8	2.9%	16.4	4.3%	3.2	0.9%	0.0	0.0%	13.7	3.6%	24.2	6.4%
5	1056.6	40.1	3.8%	53.8	5.1%	0.0	0.0%	39.6	3.7%	67.6	6.4%	103.1	9.8%

To evaluate between-lot imprecision, six extracted stool samples of various concentrations of calprotectin were tested for five days in five replicates and three lots, for a total of 75 fCAL ELISA test results per sample. The mean fCAL ELISA test result was computed and the within-run, between-run, between-day, and total standard deviations (SD) and associated coefficients of variation (%CV) were calculated.

Sample	Mean (µg/g)	Within-run		Between-day		Between-reader		Between-operator		Between-lot		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	46.4	2.5	5.5%	0.5	1.1%	2.3	5.0%	1.5	3.2%	2.4	5.3%	4.5	9.7%
2	105.5	2.5	2.4%	1.4	1.4%	2.6	2.4%	0.8	0.8%	2.1	2.0%	4.5	4.2%
3	133.6	5.0	3.8%	1.9	1.4%	2.2	1.7%	0.0	0.0%	4.2	3.2%	7.2	5.4%
4	178.5	6.3	3.5%	0.0	0.0%	0.7	0.4%	2.3	1.3%	6.3	3.5%	9.2	5.2%
5	435.2	12.4	2.9%	7.5	1.7%	0.0	0.0%	0.0	0.0%	18.1	4.2%	23.2	5.3%
6	1476.1	48.4	3.3%	88.6	6.0%	0.0	0.0%	32.2	2.2%	31.4	2.1%	110.6	7.5%

To evaluate extraction reproducibility, stool samples were tested in 10 extractions and measured in duplicates per extraction, for a total of 20 fCAL ELISA test results obtained per sample. For each sample, the means fCAL ELISA test results were calculated and the within-extraction, between-extraction, and total standard deviations (SD) and associated coefficients of variation (%CV) were calculated.

Sample	Mean (µg/g)	Within-extraction		Between-extraction		Total	
		SD	%CV	SD	%CV	SD	%CV
1	51.2	4.5	8.9%	7.8	15.2%	9.0	17.6%
2	88.3	6.6	7.5%	13.3	15.0%	14.8	16.8%
3	66.8	10.6	15.8%	3.7	5.5%	11.2	16.7%
4	179.3	16.8	9.4%	32.8	18.3%	36.8	20.5%
5	366.1	22.4	6.1%	32.3	8.8%	39.3	10.7%
6	327.4	15.4	4.7%	26.9	8.2%	31.0	9.5%
7	1783.7	198.3	11.1%	262.0	14.7%	328.6	18.4%

b. Linearity/assay reportable range:

Linearity: A linearity study was conducted in accordance with CLSI guideline EP6-A. A total of seven samples were assessed for linearity evaluation in the full range of the assay from 30 µg/g to 1,800 µg/g calprotectin. The BÜHLMANN fCAL ELISA results are linear for the claimed measuring range of 30 to 1,800 µg/g.

Sample	Range (µg/g)	Slope (95%CI)	Intercept (95% CI)	R^2
1	49.3–286.2	0.977 (0.948, 1.006)	7.3 (3.0, 11.6)	0.996
2	41.5–323.2	1.027 (1.006, 1.047)	-10.0 (-13.4, -6.6)	0.998
3	27.6–216.4	1.033 (0.994, 1.072)	-10.6 (-15.4, -5.8)	0.993
4	21.3–1,544.6	1.032 (1.013, 1.051)	11.7 (-4.1, 27.5)	0.996
5	22.8–1,932.0	0.963 (0.949, 0.977)	-21.1 (-35.8, -6.4)	0.998
6	26.2–2,096.2	0.969 (0.953, 0.985)	-31.6 (-50.6, -12.6)	0.997
7	39.0–1,830.2	1.012 (0.980, 1.044)	-1.1 (-32.2, 30.1)	0.994

Accuracy/Recovery: To evaluate the accuracy of the BÜHLMANN fCAL ELISA, seven stool specimen extracts supplemented with Incubation Buffer (B-CAL-IB) at 10% specimen volume, covering the reportable range of the assay, were each tested in triplicates to establish a baseline result. Each specimen extract was then spiked by 10% specimen extract volume with calibrator material (1,800 µg/g) to obtain a calculated spike value of 180 µg/g.

Specimen Extract	Mean Baseline Result (µg/g)	Expected Post- Spike Result (µg/g)	Observed Post-Spike Result (µg/g)	Recovery (%)
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

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Traceability: No international reference material or reference measurement procedures are available for calprotectin. Therefore, metrological traceability to

international (SI) units cannot be established. The BÜHLMANN fCAL ELISA is traceable to an internal standard generated from pooled human serum. The value of the internal standard was initially assigned using a primary standard material made from recombinant calprotectin. The final value of the internal standard value was established over multiple runs and reagent lots of the BÜHLMANN fCAL ELISA.

Stability:

Real-time reagent stability: Three reagent lots and three stool extracts (one below 80 µg/g, one between 80 µg/g and 160 µg/g, and one above 160 µg/g) were used to establish reagent stability. Reagents were stored at 2–8°C throughout the study. Stool extracts were stored in accordance with the instructions for use. The results of the study support the claim that BÜHLMANN fCAL ELISA reagents are stable for 24 months at 2–8°C.

Transport stability: Two reagent lots, two stool samples, and two levels of control material were used. Reagents were stored at 28°C and 37°C to mimic temperature conditions that may be experienced during shipping. Reagent/sample/control combinations were tested in duplicates at baseline, and at seven days, 14 days, and 21 days post-baseline. The results of the study support the claim that BÜHLMANN fCAL ELISA reagents are stable for 21 days at 28°C and five days at 37°C.

Open vial stability: Four reagent lots, four stool samples, and two levels of control material were used. Reagents were opened and reconstituted prior to testing at baseline, and stored at 2–8°C for use at two months and six months after the baseline time point. The results of the study support the claim that BÜHLMANN fCAL ELISA is stable for six months in open kit/in-use.

Analyte stability: Analyte stability was evaluated under the following storage conditions of:

- raw stool specimens at 2–8°C
- stool extracts at -20°C and 2–8°C
- stool extracts post freeze/thaw cycles

The demonstrated stability duration is three days at 2–8°C for raw stool specimen, three years at -20°C for stool extract, seven days at 2–8°C for stool extract, and three freeze (-20°C) /thaw (room temperature) cycles.

d. Detection limit:

Limit of Blank (LoB)

Four blank samples (incubation buffer spiked with extraction buffer) were tested over a three-day period using two reagent lots, with five test determinations obtained from each sample on each day using each reagent lot. The study design generated a total of 60 test determinations with each reagent lot and the LoB was estimated as the 95th percentile of the distribution of test results using a non-parametric method. The LoB

value was determined to be 8.3 μg/g.

Limit of Detection (LoD)
Four specimen extracts with low levels of calprotectin, i.e., samples with concentrations between one and five times of the estimated LoB, were tested over a three-day period using two reagent lots, with five test determinations obtained from each extract on each day using each reagent lot and the pooled standard deviation (SDL) was computed as the weighted average of the standard deviations across the four samples. The LoD for each reagent lot was then computed using the formula LoD = LoB + Cp x SDL, where Cp is the 95th percentile of the standard normal distribution, corrected for the use of the observed sample standard deviations. The LoD value was determined to be 12.6 μg/g.

Limit of Quantitation (LoQ)
Each extract of four specimen extracts was tested over a three-day period using two reagent lots with five test determinations obtained from each extract on each day using each reagent lot. The mean test result and associated coefficient of variation (%CV) were computed for each specimen extract as tested with each reagent lot. The LoQ value was determined to be 30.0 μg/g.

e. Analytical specificity:
A total of 19 potential interferents were investigated in this study, including six microorganisms and 13 chemical interferents (e.g., oral pharmaceuticals and nutritional supplements) with four samples with calprotectin concentrations at: near 30.0 μg/g, 100.0 μg/g, 200.0 μg/g, and 500.0 μg/g.

Microorganism interferences:

Microorganism	**Concentration (cfu/mL)**
Escherichia coli	9.5×10^7
Salmonella enterica subsp. enterica	1.0×10^9
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

Drugs and endogenous factor interferences:

Trade name	Active component	Solvent	Concentration (mg/50 mg stool)
gyno-Tardyferon	Iron (II) sulfate	HCl / NaOH	0.11
Prednisone	Prednisone	DMSO	0.31
Imurek	Azathioprine	DMSO	0.19
Salofalk	Mesalamine; 5-ASA	DMSO	5.21
Agopton	Lansoprazole	Dimethylformamide	0.18
Asacol	Mesalamine; 5-ASA	DMSO	2.50
Vancocin	Vancomycin	H_2Odd	2.00
Sulfamethoxazol	Sulfamethoxazole	DMSO	1.60
Trimethoprim	Trimethoprim lactate	DMSO / Exbuffer	0.35
Ciproxine	Ciprofloxacin	solvent from manufacturer / H_2Odd	1.25
Vitamin E	DL-α Tocopherol	H_2O + Tween	0.30
Bion 3	Multivitamin	HCl / NaOH	1.06
Hemoglobin	Hemoglobin	H_2Odd	1.25

The tested potential interferents exhibited a change of <10% in the mean fCAL ELISA test results when added to stool specimen extracts at various levels of fecal calprotectin.

f. Assay cut-off:

The assay cut-offs for the BÜHLMANN fCAL ELISA follow:

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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 indicated

2. Comparison studies:

a. Method comparison with predicate device:

A total of 371 raw stool samples obtained for the clinical study were also tested for analysis using BÜHLMANN fCAL ELISA and the predicate assay (Calprest NG assay) in accordance with each assay's instructions for use. Method comparison

analysis was performed using cut-offs of both assays and the number of study subjects at each level.

		Subject number in Calprest NG assay range (µg/g)			
		< 50	**50–120**	**> 120**	**Total**
Subject number in BÜHLMANN fCAL ELISA range (µg/g)	**< 80**	198	4	1	203
	80–160	28	16	0	44
	> 160	14	29	81	124
Total		240	49	82	371

Estimates of percent agreement, positive percent agreement (PPA) and negative percent agreement (NPA), between BÜHLMANN fCAL ELISA and Calprest NG assay results area shown below:

Metric	**Estimate**	**95% C.I.**
PPA at 80µg/g cutoff	126/131 = 96.2%	[91.3%, 98.7%]
NPA at 80µg/g cutoff	198/240 = 82.5%	[77.1%, 87.1%]
PPA at 160µg/g cutoff	81/82 = 98.8%	[93.4%, 100%]
NPA at 160µg/g cutoff	246/289 = 85.1%	[80.5%, 89.0%]

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical Sensitivity/clinical specificity:

The study subject population consisted of 478 subjects including 415 adults (above age 21) and 63 pediatric (age between 4 and 21) patients. Per standard clinical practice, all patients presenting with signs and symptoms suggestive of IBS or IBD, including patients previously diagnosed with IBD and referred for endoscopic investigation due to a suspected flare or routine exam, were enrolled and referred for endoscopy. Each eligible study subject provided one stool sample for analysis using the fCAL ELISA at least one day prior to any scheduled endoscopy procedure or no more than three days after an endoscopy procedure. The final clinical diagnosis of IBD, IBS, or other GI disorder was determined by the clinical investigator based on

the results of the endoscopy as well as other clinical findings, e.g. histology and Rome III criteria. The final diagnoses of the subjects were as follows: 135 IBD (102 adult and 33 pediatric), 130 IBS (102 adult and 28 pediatric), and 72 other gastrointestinal disorders other than IBD or IBS (70 adults and 2 pediatric). Thirteen clinical sites in the U.S. enrolled and determined the final clinical diagnoses. The fecal samples were tested with the BÜHLMANN fCAL ELISA in three clinical laboratories.

Final Diagnosis	**Subject number and percent in fCAL ELISA range (µg/g)**			
	<80	**80-160**	**>160**	**Total**
IBD	9 (6.7%)	12 (8.9%)	114 (84.4%)	135 (100%)
IBS	94 (72.3%)	17 (13.1%)	19 (14.6%)	130 (100%)
GI Other	48 (66.7%)	10 (13.9%)	14 (19.4%)	72 (100%)

IBD vs. non-IBD comparison:
Estimates of sensitivity and specificity along with 95% confidence intervals were calculated for the BÜHLMANN fCAL ELISA as an aid in the discrimination between IBD and non-IBD (IBS and other gastrointestinal disorders) in all subjects (≥ 4 years of age), using test cutoffs at 80 and 160 µg/g.

Positive cases considered at ≥80 µg/g		**Clinical Diagnosis**		**Total**
		IBD	**Non-IBD**	
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%)				

Positive cases considered at ≥160 µg/g		**Clinical Diagnosis**		**Total**
		IBD	**Non-IBD**	
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%)				

IBD vs. IBS diagnosis:
Estimates of sensitivity and specificity along with 95% confidence intervals were

calculated for the BÜHLMANN fCAL ELISA as an aid in the discrimination between IBD and IBS in all subjects (≥4years of age), using test cutoffs at 80 and 160 µg/g.

Positive cases considered at ≥80 µg/g		**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%)				

Positive cases considered at ≥160 µg/g		**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%)				

b. Other clinical supportive data (when a. is not applicable):

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

Not applicable

N. Proposed Labelling:

The labelling 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.