510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K193115

B Applicant

EUROIMMUN US, Inc.

C Proprietary and Established Names

EUROIMMUN Anti-BP230-CF ELISA (IgG)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
OEG	Class II	21 CFR 866.5660 - Multiple Autoantibodies Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

New Device

B Measurand:

Anti-Bullous Pemphigoid (BP) 230 IgG Autoantibodies

C Type of Test:

Qualitative or Semi-Quantitative, ELISA

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:
The EUROIMMUN Anti-BP230-CF ELISA (IgG) test kit is intended for the qualitative or semi-quantitative determination of immunoglobulin class IgG antibodies against BP 230 in human serum and plasma (K3-EDTA, Li+-heparin, Na+-citrate). It is used as an aid in the diagnosis of bullous pemphigoid, in conjunction with other laboratory and clinical findings.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

D Special Instrument Requirements:
Microtiter plate reader capable of measuring optical densities at 450 nm and a reference wavelength of between 620 nm and 650 nm

IV Device/System Characteristics:

A Device Description:
The Anti-BP230-CF ELISA (IgG) test kit is composed of six ready-to-use microplate strips containing eight individual break-off wells in a frame, three levels of calibrators (2 mL each, at 2, 20, and 200 RU/mL human IgG), positive and negative controls (2.0 mL each), 1x12 mL bottle peroxidase-labelled rabbit anti-human IgG, 1x100 mL bottle sample buffer, 1x12 mL bottle TMB/H_2O_2 chromogen/substrate, 1x12 mL bottle stop solution, and a 1x100 mL bottle of 10X concentrated wash solution.

B Principle of Operation:
The test kit contains six microplate strips each with eight break-off reagent wells coated with BP230-CF. Diluted patient samples (1:101 in the sample buffer), calibrators and controls are added to the wells and incubated for 30 minutes at 18–25°C. The wells are washed to remove any unbound proteins and non-specific antibodies and rabbit anti-human IgG HRP enzyme conjugate is added to each well. After incubation for 30 minutes at 18–25°C, the wells are washed to remove any unbound HRP enzyme conjugate and 3,3,5,5 tetramethylbenzidine (TMB) enzyme substrate is added. After an additional incubation for 15 minutes at 18–25°C, a stop solution is added. The test strips are placed in a microplate reader and the optical density of the color is measured at a wavelength of 450 nm and a reference wavelength between 620 nm and 650 nm within 30 minutes. The amount of antigen-specific bound antibody is proportional to the color intensity.

V Substantial Equivalence Information:

A Predicate Device Name(s):
MESACUP BP180 ELISA Kit and MESACUP BP230 ELISA Kit

B Predicate 510(k) Number(s):
K071961

C Comparison with Predicate(s):

Device & Predicate Device(s):	K193115	K071961
Device Trade Name	EUROIMMUN Anti-BP230-CF ELISA (IgG)	MESACUP BP180 ELISA Kit and MESACUP BP230 ELISA Kit
General Device Characteristic Similarities		
Intended Use / Indications For Use	The EUROIMMUN Anti-BP230-CF ELISA (IgG) test kit is intended for the qualitative or semi-quantitative determination of immunoglobulin class IgG antibodies against BP230 in human serum and plasma (K3-EDTA, Li+-heparin, Na+-citrate). It is used as an aid in the diagnosis of bullous pemphigoid, in conjunction with other laboratory and clinical findings.	The MESACUP BP180 Test is a semi-quantitative, enzyme-linked immunosorbent assay (ELISA) for the detection of anti BP180 antibodies in human serum. The MESACUP BP180 Test is intended for in-vitro diagnostic use as an aid in the diagnosis of bullous pemphigoid in conjunction with other laboratory and clinical findings. Patients with bullous pemphigoid are known to have either BP180 or BP230 or both types of antibodies in serums. It is recommended that each patient be tested for both BP180 and BP230 antibodies. The MESACUP BP230 Test is a semi-quantitative, enzyme-linked immunosorbent assay (ELISA) for the detection of anti BP230 antibodies in human serum. The MESACUP BP230 Test is intended for in-vitro diagnostic use as an aid in the diagnosis of bullous pemphigoid in conjunction with other laboratory and clinical findings. Patients with bullous pemphigoid are known to have either BP180 or BP230 or both types of antibodies in serums. It is recommended that each patient be tested for both BP180

		and BP230 antibodies.
Technology	ELISA, photometric	Same
Assay Platform	48-well microtiter plates	Same
Substrate	TMB / H_2O_2	Same
Wash Buffer	10x concentration	Same
Sample Dilution	1:101	Same
General Device Characteristic Differences		
Assay Type	Qualitative or semi-quantitative	Semi-quantitative
Sample Matrix	Serum and plasma	Serum
Antigen	Recombinant purified C-terminal section of the human 230 kDa BP antigen	Recombinant purified BP230-N and BP230-C antigen
Conjugate	Peroxidase-labelled anti-human IgG (rabbit)	Peroxidase-labelled anti-human IgG (goat)
Controls	1 Positive Control 1 Negative Control	No controls supplied (recommendation that user create own controls)
Calibrators	3 Calibrators: 2, 20 and 200 RU/mL	2 Calibrators: 0 and 100 U/mL
Measuring Range	2.75–200 RU/mL	5–150 U/mL
Reported Results	Ratio (Qualitative) RU/mL (Semi-quantitative)	U/mL (Semi-quantitative)
Interpretation	Ratio result*: <1.0: negative ≥1.0: positive RU/mL result: <20: negative ≥20: positive	U/mL result: <9: negative ≥9: positive

* Ratio = OD of sample / OD of calibrator 2 (20 RU/mL)

VI Standards/Guidance Documents Referenced:

- CLSI EP6-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
- CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
   All studies were evaluated based on semi-quantitative measurement (RU/mL) and qualitative interpretation (positive: ratio ≥1.0; negative: ratio <1.0) calculated by the ratio of OD of the sample to the OD of the cut-off, Calibrator 2 (20 RU/mL).

   Precision: Single-site precision was investigated using six native patient serum samples with values at different points on the calibration curve. A total of 80 determinations per sample were obtained in 40 different runs on 20 different days (with two runs per day and two replicates per run). For semi-quantitative determination, the standard deviations (SD) and coefficients of variation (CV) of repeatability (within-run), between-run, between-day, and within-lab (total) imprecision were calculated and the results are summarized in the following table:

		Within-Run		Between-Run		Between-Day		Total	
Sample	Mean (RU/mL)	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	4.7	0.4	9.5	0.3	6.4	0.3	5.9	0.6	12.9
2	14.9	0.8	5.3	1.1	7.7	0.9	5.9	1.6	11.0
3	19.0	1.6	8.2	0.7	3.5	1.2	6.3	2.1	11.0
4	24.8	1.7	6.9	1.4	5.5	1.4	5.7	2.6	10.5
5	109.0	3.4	3.1	5.0	4.6	2.9	2.7	6.7	6.2
6	130.3	4.9	3.8	5.4	4.2	3.7	2.9	8.2	6.3

   The single-site imprecision was analyzed using qualitative determination, and the following results were obtained:

Sample	Mean Ratio	Range of Ratio	Expected Result	Pos/Neg	Agreement (%)
1	0.3	0.3–0.4	Negative	0 / 80	100.0
2	0.8	0.6–0.9	Negative	0 / 80	100.0
3	1.0*	0.7–1.1	Negative	18 / 62	77.5
4	1.1	1.0–1.2	Positive	76 / 4	95.0
5	3.3	2.6–3.7	Positive	80 / 0	100.0
6	3.8	3.4–4.3	Positive	80 / 0	100.0

   ***** mean ratio rounded from 0.95

   Lot-to-Lot Reproducibility: Between-lot reproducibility was investigated using nine native patient serum samples with values at different points on the calibration curve. A total of 90 determinations were obtained per sample by testing with three lots on five different days (with two runs per day and three replicates per run). For semi-quantitative determination, the SD and %CV of within-run, between-run, between-lot and total imprecision were calculated, and the results are summarized in the following table:

		Within-Run		Between-Run		Between-Lot		Total	
Sample	**Mean (RU/mL)**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
1	4.5	0.5	11.6	0.6	14.2	0.1	3.0	0.8	18.6
2	14.1	1.8	12.5	0.8	5.7	0.4	2.5	2.8	14.9
3	14.1	1.1	7.6	1.0	7.3	0.0	0.0	1.5	10.5
4	16.9	0.7	3.9	1.0	5.9	0.6	3.3	1.5	8.7
5	17.8	0.8	4.6	1.1	6.0	0.5	3.0	1.5	8.7
6	18.1	1.3	7.3	1.7	9.5	0.6	3.5	2.6	14.4
7	22.0	1.7	7.8	0.7	3.1	1.7	7.7	2.6	11.9
8	102.7	5.1	4.9	5.4	5.3	0.0	0.0	8.7	8.5
9	124.4	7.3	5.9	8.2	6.6	0.0	0.0	11.6	9.4

Between-lot reproducibility was analyzed using qualitative determination, and the following results were obtained:

Sample	Mean Ratio	Range of Ratio	Expected Result	Pos/Neg	Agreement (%)
1	0.3	0.2–0.4	Negative	0 / 90	100.0
2	0.7	0.5–1.0	Negative	0 / 90	100.0
3	0.7	0.6–0.9	Negative	0 / 90	100.0
4	0.9	0.7–1.0	Negative	0 / 90	100.0
5	0.9	0.7–1.0	Negative	5/ 85	94.4
6	0.9	0.7–1.1	Negative	20 / 70	77.8
7	1.0	0.9–1.2	Positive	62 / 28	68.9
8	2.8	2.3–3.5	Positive	90 / 0	100.0
9	3.3	2.6–4.1	Positive	90 / 0	100.0

Site-to-Site Reproducibility: Between-site reproducibility was investigated using six native patient serum samples with values at different points on the calibration curve. A total of 90 determinations were obtained per sample by testing at three sites for five different days (with two runs per day and three replicates per run). For semi-quantitative determination, the SD and %CV for within-run, between-run, between-site and total reproducibility were calculated, and the results are summarized in the following table:

		Within-Run		Between-Run		Between-Site		Total	
Sample	**Mean (RU/mL)**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
1	4.8	0.3	7.2	0.4	7.7	0.3	5.7	0.6	12.3
2	16.8	0.9	5.6	0.8	4.5	1.2	7.4	1.9	11.1
3	18.0	0.9	5.0	0.6	3.5	1.5	8.3	2.0	11.0
4	20.9	1.9	8.9	2.0	9.5	2.4	11.3	3.6	17.4
5	91.6	5.2	5.7	4.2	4.5	8.5	9.3	11.0	12.0
6	128.3	5.7	4.5	6.5	5.1	9.5	7.4	13.6	10.6

Between-site reproducibility was analyzed using qualitative determination, and the following results were obtained:

Sample	Mean Ratio	Range of Ratio	Expected Result	Pos / Neg	Agreement (%)
1	0.3	0.2–0.4	Negative	0 / 90	100.0
2	0.9	0.6–1.0	Negative	1 / 89	98.9
3	0.9	0.7–1.1	Negative	10 / 80	88.9
4	1.0	0.7–1.2	Positive	49 / 41	54.4
5	2.7	2.2–3.5	Positive	90 / 0	100.0
6	3.5	2.7–4.3	Positive	90 / 0	100.0

2. Linearity:
   The linearity of EUROIMMUN Anti-BP230-CF ELISA was evaluated based on the CLSI guideline EP06-A. The sample preparations covered the range of 2.0 to 202.33 RU/mL using two sets of samples. Each set included 11 sample dilutions and was measured in a run with four replicates per sample dilution; the mean of the four replicates for each sample was calculated. The linear regression analysis of observed value (RU/mL) vs. expected value (RU/mL) of samples was performed. The results support that the EUROIMMUN Anti-BP230-CF ELISA assay was linear for the claimed measuring range, 2.75–200 RU/mL.

3. Analytical Specificity/Interference:
   To investigate the influence from the potential endogenous interferents, three samples at different anti-BP230-CF antibody concentrations (negative, low positive, high positive) were prepared for testing rheumatoid factor and five samples with different anti-BP230-CF antibody concentrations (two negatives, one low positive, and two high positives) were prepared for testing hemoglobin, triglycerides, and bilirubin. The recovery in relation of the spiked sample with interferent to the unspiked sample without interferent was calculated. No interference (the recovery within 85–115%) was observed for concentrations of up to 1,000 mg/dL for hemoglobin, 2,000 mg/dL for triglycerides, 40 mg/dL for bilirubin, and 1,000 IU/mL for rheumatoid factor.

   For the potential exogenous interferents, four test samples with different anti-BP230-CF antibody concentrations (two negatives, one low positive, one high positive) were spiked with potential exogenous interferent substances (mycophenolic acid, cyclophosphamide monohydrate, prednisone, and azathioprine). The recovery in relation of the spiked sample with interferent to the unspiked sample without interferent was calculated. No interference (the recovery within 85–115%) was observed for concentrations of up to 4.2 mg/dL for mycophenolic acid, 54.9 mg/dL for cyclo-phosphamide monohydrate, 0.0099 mg/dL for prednisone, and 0.258 mg/dL for azathioprine.

4. Assay Reportable Range:
   The assay reportable range of the Anti-BP230-CF ELISA is 2.75 to 200 RU/mL.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):
   a. Traceability: A recognized standard or reference material for anti-BP230 antibodies is not available. The assay is calibrated in relative arbitrary units (RU/mL) in semi-quantitative mode. Alternatively, results may be given in ratios of the cut-off calibrator (Calibrator 2, 20 RU/mL) and then defined as positive or negative in qualitative mode.

b. Shelf-life Stability: In the real-time stability study for sealed products, aliquots of the reagents were stored at 2–8°C. Three different reagent lots were used for testing samples (three positive samples, calibrators and controls) at 0, 3, 6, 12, 18, and 24 months. The results of the study support a claim that the EUROIMMUN Anti-BP230-CF ELISA kit is stable for up to 12 months at 2–8°C.

c. Open-vial Reagent Stability: In the real-time stability study for open-vial products, aliquots of the reagents were opened and stored at 2–8°C. Three different reagent lots were used for testing samples (three positive samples, calibrators and controls) at 0, 3, 6, and 12 months. The results of the study support a claim that the EUROIMMUN Anti-BP230-CF ELISA reagents in open vials are stable for up to 6 months at 2–8°C.

6. Detection Limit:
Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) were determined per CLSI EP17-A2.

For LoB, a set of four native negative (blank) human samples in the range below the measuring interval was obtained from four healthy individuals. Each sample was run in 15 replicates (five replicates per run x one run per day x three days) using two lots of reagents to reach a total of 60 measurements per lot. The LoB of the Anti-BP230-CF ELISA was found to be 1.53 RU/mL.

For LoD, a set of four samples with low measurand concentrations near the lower end of the measuring interval was investigated. Each sample was run in 15 replicates (five replicates per run x one run per day x three days) using two lots to reach a total of 60 measurements per lot. The LoD of the Anti-BP230-CF ELISA was found to be 2.35 RU/mL.

For LoQ, another set of four low measurand content samples from the lower end of the measuring interval was investigated. Each sample was run in 15 replicates (five replicates per run x one run per day x three days) using two lots to reach a total of 60 measurements per lot. Based on the functional sensitivity analysis, the LoQ of the Anti-BP230-CF ELISA was defined as the lowest concentration that met %CV ≤ 20% and was found to be 2.75 RU/mL.

7. Assay Cut-Off:
The Anti-BP230-CF ELISA is determined to be negative for <20 RU/mL and positive for ≥20 RU/mL in the semi-quantitative analysis, and negative for a ratio of <1.0 and positive for a ratio of ≥1.0 in the qualitative analysis.

B Comparison Studies:

1. Method Comparison with Predicate Device:
A panel of 202 clinical samples was tested with the EUROIMMUN Anti-BP230-CF ELISA and with the MBL MESACUP BP230 ELISA (predicate) according to their respective package inserts. The samples contained 101 bullous pemphigoid, 11 pemphigoid gestationis, 15 systemic sclerosis, 20 Sjögren's syndrome, 15 rheumatoid arthritis, 20 systemic lupus erythematosus, and 20 diabetes mellitus type 1 (T1D) disease samples. Both RU/mL (semi-quantitative) and ratio (qualitative) assessments yielded the same results as shown in the following table:

Samples (N=202)		MBL MESACUP BP230 ELISA (predicate)		
		Positive	**Negative**	**Total**
EUROIMMUN Anti-BP230-CF ELISA (K193115)	Positive	44	18	62
	Negative	11	129	140
	Total	55	147	202

Sample (N=202)	No. Agreement	% Agreement	95% C.I.
Positive Agreement	44 / 55	80.0	67.0–89.6
Negative Agreement	129 / 147	87.8	81.3–92.6
Overall Agreement	173 / 202	85.6	80.0–90.2

The performance of the EUROIMMUN Anti-BP230-CF ELISA and MBL MESACUP BP230 ELISA assay was further analyzed by comparing the test result to clinical diagnosis using this sample cohort. The results are summarized in the following table.

Disease Panel	Sample (N)	EUROIMMUN Anti-BP230-CF ELISA	MBL MESACUP BP230 ELISA (Predicate)
		Positive% (n/N)	**Positive % (n/N)**
Bullous pemphigoid	101	57.4 (58/101)	49.5 (50/101)

Disease Panel	Sample (N)	EUROIMMUN Anti-BP230-CF ELISA	MBL MESACUP BP230 ELISA (Predicate)
		Negative% (n/N)	**Negative% (n/N)**
Pemphigoid gestationis	11	90.9 (10/11)	90.9 (10/11)
Systemic sclerosis	15	93.3 (14/15)	100.0 (15/15)
Sjögren's syndrome	20	95.0 (19/20)	90.0 (18/20)
Rheumatoid arthritis	15	100.0 (15/15)	100.0 (15/15)
Systemic lupus erythematosus	20	100.0 (20/20)	95.0 (19/20)
Diabetes mellitus type 1	20	95.0 (19/20)	95.0 (19/20)
Total (non-BP)	**101**	**96.0 (97/101)**	**95.0 (96/101)**

2. Matrix Comparison:
The usability of plasma in the Anti-BP230-CF ELISA was investigated using 31 sample sets each consisting with matched serum and corresponding plasma matrices (K3-EDTA, Li+-heparin, Na+-citrate). The samples covered relevant analyte levels across the measuring interval. Passing-Bablok regression was performed for the comparison of plasma to serum.

The results in RU/mL are shown in the table below.

	EDTA Plasma	Heparin Plasma	Citrate Plasma
N	29	30	30
Sample range (RU/mL) (serum)	4.46–197.62	4.28–197.62	4.28–197.62
Sample range (RU/mL) (plasma)	3.84–188.65	3.12–91.19	3.03–183.73
Slope (95% C.I.)	0.99 (0.90–1.06)	0.98 (0.94–1.01)	0.98 (0.93–1.03)
Intercept (95% C.I.)	0.71 (-2.00–8.47)	1.18 (-1.66–3.91)	-0.36 (-1.73–3.64)
R^2	0.95	0.99	0.99

The results in Ratio are shown in the table below.

	EDTA Plasma	Heparin Plasma	Citrate Plasma
N	31	31	31
Sample range (Ratio) (serum)	0.20–5.23	0.20–5.23	0.20–5.23
Sample range (Ratio) (plasma)	0.22–5.29	0.21–4.98	0.21–5.05
Slope (95% C.I.)	1.00 (0.93–1.06)	0.98 (0.94–1.03)	0.98 (0.94–1.02)
Intercept (95% C.I.)	-0.01 (-0.09–0.14)	0.02 (-0.06–0.14)	-0.00 (-0.06–0.12)
R^2	0.96	0.99	0.99

C Clinical Studies:

1. Clinical Sensitivity and Clinical Specificity:
   A clinical study was performed using a total of 421 clinically characterized samples (168 from BP patients and 253 from patient with other control diseases). The samples were tested with the EUROIMMUN Anti-BP230-CF ELISA (IgG). The clinical sensitivity and specificity of the assay were evaluated based on the test results in semi-quantitative (RU/mL) and qualitative (ratio) determinations. Both RU/mL (semi-quantitative) and ratio (qualitative) assessments yielded the same results as shown in the following table:

Clinical Sensitivity				
Panel	**N (men, women)**	**Mean Age (range)**	**Positive (%) (n/N)**	**95% C.I.**
Bullous pemphigoid	168 (73, 95)	78 (46 – 98)	50.6 (85/168)	42.8 – 58.4

Clinical Specificity				
Panel	**N (men, women)**	**Mean Age (range)**	**Negative (%) (n/N)**	**95% C.I.**
Pemphigus vulgaris	15 (9, 6)	50 (30 – 78)	100.0 (15/15)	78.2 – 100.0
Pemphigus foliaceus	15 (8, 7)	63 (34 – 86)	93.3 (14/15)	68.1 – 99.8
Linear IgA dermatosis	17 (10, 7)	54 (2 – 102)	100.0 (17/17)	80.5 – 100.0
Epidermolysis bullous acquisita	17 (4, 13)	51 (16 – 92)	88.2 (15/17)	63.6 – 98.5
Sjögren's syndrome	20 (1, 19)	53 (16 - 77)	95.0 (19/20)	75.1 – 99.9
Systemic lupus erythematosus	20 (5, 15)	42 (19 – 78)	100.0 (20/20)	83.2 – 100.0
Systemic sclerosis	15 (5, 10)	62 (23 – 87)	93.3 (14/15)	68.1 – 99.8
Rheumatoid arthritis	15 (5, 10)	63 (33 – 86)	100.0 (15/15)	78.2 – 100.0
Diabetes mellitus type 1	20 (11, 9)	39 (18 – 62)	95.0 (19/20)	75.1 – 99.9
Hashimoto's thyroiditis	19 (1, 18)	36 (10 – 64)	100.0 (19/19)	82.4 – 100.0
Dermatitis herpetiformis	20 (10, 10)	55 (18 – 85)	100.0 (20/20)	83.2 – 100.0
Dermatomyositis	20* (2, 5)	47 (24 – 62)	100.0 (20/20)	83.2 – 100.0
Multiple sclerosis	20 (7, 13)	Unknown	100.0 (20/20)	83.2 – 100.0
Malignancy **	20 (8, 12)	63 (19 – 88)	100.0 (20/20)	83.2 – 100.0
TOTAL	**253**		**97.6 (247/253)**	**94.9 – 99.1**

* gender information was unknown for 13 dermatomyositis samples

** 10 leukemia, 5 lymphoma, and 5 lung cancer samples were included

2. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable

D Clinical Cut-Off:

See assay cut-off

E Expected Value/Reference Range:

The expected value for the Anti-BP230-CF ELISA assay in the normal population is negative. Anti-BP230 antibodies were analyzed with the Anti-BP230-CF ELISA (IgG) using a panel of 438 sera from normal healthy adult blood donors (including 286 men and 152 women with an average age of 40 years old, ranging from 22 to 67 years). The samples were assayed according to the package insert and the results are summarized in the following table.

Healthy Blood Donors (n = 438)		
	Semi-quantitative (RU/mL)	**Qualitative (Ratio)**
Positives (n)	9	9
Negatives (n)	429	429
Prevalence % (95% C.I.)	2.1 (1.0 – 3.9)	2.1 (1.0 – 3.9)
Range (min, max)	<2.75 to 94.4	0.004 to 3.3
Mean	8.6	0.4
Median	6.5	0.3

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.