510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K180607

B. Purpose for Submission:

New device

C. Measurand:

Steroid 21-Hydroxylase Antibody (21-OHAb)

D. Type of Test:

Manual enzyme-linked immunosorbent assay, qualitative

E. Applicant:

KRONUS Market Development Associates, INC.

F. Proprietary and Established Names:

KRONUS Steroid 21-Hydroxylase Autoantibody (21-OHAb) ELISA Kit

G. Regulatory Information:

1. Regulation section:

   21 CFR § 866.5660, Multiple autoantibody immunological test system

2. Classification:

   Class II

3. Product code:

   PCG, 21-Hydroxylase Antibody (21-OHAb) antibody assay

4. Panel:

   Immunology (82)

H. Intended Use:

1. Intended use:

   The KRONUS Steroid 21-Hydroxylase Autoantibody (21-OHAb) ELISA Kit is for the qualitative determination of antibodies to steroid 21-hydroxylase (21-OH) in human serum. The Steroid 21-Hydroxylase Autoantibody (21-OHAb) ELISA Kit is useful as an aid in the diagnosis of autoimmune adrenal disease, whether expressed as autoimmune Addison's disease (isolated) or Addison's disease as part of the more complex autoimmune polyglandular syndrome (APS), type I or II. The assay result is to be used in conjunction with other clinical and laboratory findings and is not a substitute for functional testing required to diagnose adrenal insufficiency.

2. Indication for use:

   Same as intended use

3. Special conditions for use statement:

   For prescription use only.

4. Special instrument requirements:

   Microtiter plate reader capable of measuring a 96 well plate at 405 nm

I. Device Description:

The KRONUS Steroid 21-Hydroxylase Autoantibody (21-OHAb) ELISA Kit consists of the following components:

1. Recombinant human 21-OHAb-coated ELISA strip wells, 96 wells in total and supplied as 12 strips of eight wells in a frame and sealed in a foil pouch with desiccant
2. Reference Preparation,1 x 0.7 mL (ready to use)
3. Kit Negative Control,1 x 0.7 mL (ready to use)
4. Kit Positive Control 1 and 2 (see label for ranges), 2 x 0.7 mL (ready to use)
5. 21-OH Reaction Enhancer (colored red), 1 x 6 mL (ready to use)
6. 21-OH Biotin (lyophilized), 3 x 5.5 mL (reconstitute immediately prior to use)
7. 21-OH Biotin Reconstitution Buffer, 2 x 10 mL (ready to use)
8. Streptavidin Peroxidase (SA-POD), 1 x 0.7 mL (dilute SA-POD 1:20 before use)
9. Streptavidin-Peroxidase Diluent, 1 x 15 mL (ready to use)
10. Tetramethylbenzidine Peroxidase Substrate (TMB), 1 x 15 mL (ready to use)
11. Stop solution (contains 0.25M H_2SO_4), 1 x 12 mL (ready-to-use)
12. Concentrated Wash Solution 1 x 125 mL (dilute 1:10 with deionized water before use)

J. Substantial Equivalence Information:

1. Predicate device name and 510(k) number:

   KRONUS 21-OHAb RIA Assay Kit (K121046)

2. Comparison with predicate(s):

Similarities		
Item	**Candidate Device** KRONUS 21-OHAb ELISA Kit	**Predicate Device** KRONUS 21-OHAb RIA Assay Kit
Intended Use	The KRONUS Steroid 21-Hydroxylase Autoantibody (21-OHAb) ELISA Kit is for the qualitative determination of antibodies to steroid 21-hydroxylase (21-OH) in human serum. The Steroid 21-Hydroxylase Autoantibody (21-OHAb) ELISA Kit is useful as an aid in the diagnosis of autoimmune adrenal disease, whether expressed as autoimmune Addison's disease (isolated) or Addison's disease as part of the more complex autoimmune polyglandular syndrome (APS), type I or II. The assay result is to be used in conjunction with other clinical and laboratory findings and is not a substitute for functional testing required to diagnose adrenal insufficiency.	Same
Analyte	Steroid 21-Hydroxylase autoantibodies	Same
Sample Matrix	Serum	Same
Incubation time	Overnight (16–20 hours)	Same

Differences		
Item	**Candidate Device** KRONUS 21-OHAb ELISA Kit	**Predicate Device** KRONUS 21-OHAb RIA Assay Kit
Methodology	Autoantibodies to 21-OH bind to 21-OH -biotin, are detected by a colorimetric reaction with streptavidin-peroxidase and	Autoantibodies to 21-OH react with I^{125}-labeled 21-OH tracer, are precipitated with Protein A, and read off a

Differences		
Item	**Candidate Device** KRONUS 21-OHAb ELISA Kit	**Predicate Device** KRONUS 21-OHAb RIA Assay Kit
	tetramethyl benzidine and read off a reference preparation	calibration curve
Method/Principle	Enzyme-linked immunosorbent assay (ELISA)	Radioimmunoassay (RIA)
Assay format	Qualitative	Semi-quantitative
Detection Equipment	Plate Reader	Gamma counter
Cut-off	Positive: ≥ 45 Negative: < 45	Positive: > 1 U/mL Negative: ≤ 1 U/mL

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

- CLSI guideline EP12-A2, User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline–Second Edition
- CLSI guideline EP07-A2, Interference Testing in Clinical Chemistry - Second Edition
- CLSI guideline C28-A3c, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline- Third Edition

L. Test Principle:

The KRONUS Steroid 21-Hydroxylase Autoantibody (21-OHAb) ELISA Kit depends on the divalent properties of the Steroid 21-Hydroxylase autoantibodies (21-OHAb) to form a bridge between 21-OH coated on ELISA plate wells and liquid phase 21-OH-biotin. The level of bound 21-OHAb is then quantitated by the sequential addition of streptavidin peroxidase (SA-POD) and tetramethylbenzidine (TMB; a chromogenic substrate) to produce a colorogenic reaction. Stop solution is added to halt the reaction and absorbance is read using an ELISA plate reader with absorbance at 450 nm. The absorbance of each specimen is compared to the reference preparation, allowing for an index value to be calculated from the mean value of duplicate wells as follows:

$$\text{Index} = \frac{\text{test sample absorbance at 450 nm}}{\text{reference preparation absorbance at 450 nm}} \times 100$$

Results are reported as "Negative", "Positive", or "Indeterminate". A specimen with an index value equal to or greater than the specified cut-off (i.e. ≥45) is considered positive for antibodies against 21-OH while an index value below this cut-off (i.e. <45) is considered negative for 21-OH antibodies.

Index values are calculated from the mean of duplicates. Results can be considered valid determinations if sample replicates yield the same clinical interpretation (i.e. both replicates have index values that are <45 or ≥45) and coefficient of variation does not exceed 20% for determinations calculated from duplicates with at least one index value in the range of 36–54.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

All results met the manufacturer's pre-determined acceptance criteria.

a. Precision/Reproducibility:

Intra-and inter-assay precision were determined using a panel consisting of four to seven human sera samples with mean index values that cover the complete range of results (<45=negative, ≥45=positive and near to the cut-off range of 33.8–56.3). The intra-assay imprecision is based on 20 determinations in a single run within a single day and the inter-assay based on 40 determinations (twice a day for 20 days) with each sample assayed with one reagent lot in one determination calculated from the mean of duplicates. The precision data for all samples was analyzed to generate a summary of the qualitative agreement as shown in the table below:

Intra-assay				
Panel member			**Qualitative agreement (N=20 per sample)**	
#	**Mean index value**	**Sample characterization**	**Number of positive test results / N**	**%Agreement in Dx calls**
1	5.4	Negative	0/20	100
2	35.5	Negative (near to cut-off)	0/20	100
3	48.6	Positive (near to cut-off)	19/19*	100
4	206.9	Positive	20/20	100

N: number of determinations; Dx: diagnostic

*One determination produced an 'indeterminate' result because it generated one negative and one positive replicate during the initial run. This ambiguous result was not resolved upon repeat and, therefore, it was omitted from data analysis.

Inter-assay				
Panel member			**Qualitative agreement (N=40 per sample)**	
#	**Mean index value**	**Sample characterization**	**Number of positive test results / N**	**%Agreement in Dx calls**
1	6.2	Negative	0/40	100
2	40.8	Negative (near to cut-off)	4/36*	88.9
3	51.9	Positive (near to cut-off)	38/40	95
4	66.0	Positive	40/40	100
5	249.3	Positive	40/40	100
6	425.5	Positive	40/40	100
7	476.3	Positive	40/40	100

N: number of determinations; Dx: diagnostic

* A total of four determinations produced an 'indeterminate' result because they generated one negative and one positive replicate during the initial run. These ambiguous results were not retested due to inadequate volume and were omitted from the analysis.

To evaluate lot-to-lot imprecision, a panel of eight human serum samples with mean index values that cover the complete range of results (negative, positive and near to cut-off) was assayed in two determinations (N=2; each determination calculated from the mean of duplicates) using three different kit lots. The results are summarized in the table below.

Lot-to-Lot										
Panel member			**Qualitative agreement (N=6 per sample)**							
#	**Mean index value**	**Sample characterization**	**Lot 1 (N=2)**		**Lot 2 (N=2)**		**Lot 3 (N=2)**		**Number of positive test results / N**	**%Agreement in Dx calls**
			1	**2**	**1**	**2**	**1**	**2**		
1	5.2	Negative	-	-	-	-	-	-	0/6	100
2	38.1	Negative (near to cut-off)	-	-	-	-	-	-	0/6	100
3	48.5	Positive (near to cut-off)	+	+	+	+	+	+	6/6	100
4	112.1	Positive	+	+	+	+	+	+	6/6	100
5	117.6	Positive	+	+	+	+	+	+	6/6	100
6	126.5	Positive	+	+	+	+	+	+	6/6	100

Lot-to-Lot										
Panel member			Qualitative agreement (N=6 per sample)							
#	Mean index value	Sample characterization	Lot 1 (N=2)		Lot 2 (N=2)		Lot 3 (N=2)		Number of positive test results / N	%Agreement in Dx calls
			1	2	1	2	1	2		
7	124.6	Positive	+	+	+	+	+	+	6/6	100
8	134.1	Positive	+	+	+	+	+	+	6/6	100
N: number of determinations; Dx: diagnostic										

The site-to-site reproducibility was also investigated by testing a panel of samples with mean index values that cover the complete range of results (negative, positive and near to cut-off) with one reagent lot in two determinations (N=2; each determination calculated from duplicate values) in one run at three different laboratories, including one in the United States. The results are summarized in the table below.

Site-to-Site										
Panel member			Qualitative agreement (N=6 per sample)							
#	Mean index value	Sample characterization	Site 1 (N=2)		Site 2 (N=2)		Sitet 3 (N=2)		Number of positive test results / N	%Agreement in Dx calls
			1	2	1	2	1	2		
1	29.2	Negative	-	-	-	-	-	-	0/6	100
2	43.7	Negative (near to cut-off)	-	O	-	-	+	+	2/5*	60
3	45.0	Positive (near to cut-off)	-	-	-	-	+	+	2/6	33.3
4	98.2	Positive	+	+	+	+	+	+	6/6	100
5	102.1	Positive	+	+	+	+	+	+	6/6	100
6	103.2	Positive	+	+	+	+	+	+	6/6	100
7	109.9	Positive	+	+	+	+	+	+	6/6	100
8	113.9	Positive	+	+	+	+	+	+	6/6	100
9	362.9	Positive	+	+	+	+	+	+	6/6	100
N: number of determinations; Dx: diagnostic * One determination produced an‘indeterminate’ result because it generated one negative and one positive replicate during the initial run. This ambiguous result was not resolved upon repeat and was therefore omitted (O) from data analysis.										

b. *Linearity/assay reportable range:*

Not applicable

Hook effect: Seven patient sera positive for 21-OH Ab were serially diluted in normal human serum. No hook effect was observed for index values up to 616.

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

i) Traceability and value assignment: There are no recognized standards for 21-OHAb. The Reference Preparation and positive controls are manufactured independently of each other and are prepared by diluting rabbit serum, containing antibodies against human 21-OH, in pooled normal human serum. The Reference Preparation is checked against an internally produced standard. The two Positive controls are assigned values based on the mean of 4 to 10 values (generated from separate assays). The Reference Preparation and positive controls are assayed and adjusted, if necessary, until all materials meet required specifications. Additionally, all controls and QC panels run with the assay must be within their established ranges. The Negative Control is pooled normal human serum (negative for 21-OH antibodies).

ii) Kit stability:

Closed kit stability A real-time stability study was performed using three lots of kit reagents, three lots of the Reference Preparation and three lots of Kit Controls to demonstrate unopened kit shelf-life stability from the date of manufacture. The samples tested included two positive controls and 12 patient samples that cover the complete range of results (negative, positive and near to cut-off). Results showed that a nine-month shelf life is appropriate for the kit reagents, Reference Preparation and Kit Controls.

Open kit stability A real-time stability study supports the stability of the ELISA plates after first opening of the foil pouch at six months when stored at 2 8ºC. The package insert recommends that any unused wells be placed in the self-seal plastic bag provided. Opened calibrators and controls are stable for four months. Reconstituted Biotin must be used immediately. Working concentrations of SA-POD are stable for 16 weeks. Diluted Wash Solution is stable for 12 months. Concentrated Wash Solution, Biotin Reconstitution Buffer, Diluent for SA-POD, TMB, and Stop Solution may be stored until the expiry date indicated on each respective container. The 'Storage and Stability' section of the Package Insert states "*Do not use reagents from kits with different lot numbers*".

iii) Sample stability and storage:

The package insert recommends that sera be assayed soon after separation or stored in aliquots at or below −20°C. If the serum is stored frozen, it is recommended to do so in aliquots, as subsequent freezing and thawing may lead to a loss of analyte.

d. Detection limit:

Not applicable

e. Analytical specificity:

i) Cross-reactivity:

To investigate the quality of the antigen coated on the plates to ensure a high specificity of the KRONUS 21-OHAb ELISA Kit, cross reactivity was evaluated with 170 sera from other autoimmune diseases and conditions for autoimmune primary adrenal insufficiency differential diagnosis. These Non-Target Disease Group samples were comprised of 58 Graves' Disease sera positive for TSH receptor antibodies (index values range from 8.5 to 21), eight Hashimoto's Thyroiditis sera positive for antibodies against thyroglobulin (TgAb) and /or thyroid peroxidase (TPOAb) (index values range from 11 to 18), 16 Rheumatoid arthritis sera (index values range from 9.9 to 20), nine Type 1 Diabetes Mellitus sera positive for zinc transporter 8 protein antibodies (index values range from 10 to 60), 62 Type 1 Diabetes Mellitus sera positive for glutamic acid decarboxylase antibodies (index values range from 7.2 to 409), eight Neuromyelitis Optica Spectrum Disorder sera positive for aquaporin-4 water channel antibodies (index values range from 11 to 16), and nine Systemic Lupus Erythematosus sera positive for double stranded DNA antibodies (index values range from 13 to 16).

A total of 168 of 170 specimens tested negative with the KRONUS 21-OHAb ELISA Kit. The two positive sera were as follows: one Type 1 Diabetes Mellitus serum (positive for zinc transporter 8 protein antibodies) with an index value of 60 and one Type 1 Diabetes Mellitus serum (positive for glutamic acid decarboxylase antibodies) with an index value of 409.

ii) Endogenous interference:

Interference testing was performed by using 10 to 12 samples with mean index values that cover the complete range of results (negative, positive and near to cut-off). Each sample was spiked with known quantities of the interfering substances and analyzed in five determinations (N=5) in one assay run with one kit lot. Results show that except for Intralipid, no interference was detected for each interfering substance tested at the concentration listed in the table below.

Potential interfering substance	Test dose	Sample			Qualitative agreement (N=5 per sample)	
		Number of sample tested	Mean index value	Sample Characterization	Number of positive test results / N	%Agreement in Dx calls
Bilirubin	20 mg/dL	1	12.0	Negative	0/5	100
		1	37.3	Negative (near to cut-off)	0/5	100
		1	49.0	Positive (near to cut-off)	5/5	100
		7	81.3 to 230.5	Positive	35/35	100
Intralipid	1000 mg/dL	1	6.6	Negative	0/5	100
		2	35.8 and 44.0	Negative (near to cut-off)	0/10	100
		2	45.7 and 51.1	Positive (near to cut-off)	3/7*	42.9
		7	73.1 to 185.4	Positive	35/35	100
Hemoglobin	5 mg/mL	1	6.4	Negative	0/5	100
		1	36.9	Negative (near to cut-off)	0/5	100
		1	50.1	Positive (near to cut-off)	5/5	100
		7	61.6 to 328.3	Positive	35/35	100
Biotin	14 µg/mL	3	4.1 to 5.1	Negative	0/15	100
		1	40.8	Negative (near to cut-off)	0/5	100
		1	51.6	Positive (near to cut-off)	5/5	100

		Sample			Qualitative agreement (N=5 per sample)	
		Number of sample tested	Mean index value	Number of sample tested	Mean index value	Number of sample tested
Biotin	14 µg/mL	5	62.1 to 330.5	Positive	25/25	100
Rheumatoid factor	250 U/mL	1	5	Negative	0/5	100
		2	38.5 and 40.3	Negative (near to cut-off)	10/10	100
		7	100 to 305.0	Positive	35/35	100

N: number of determinations; Dx: diagnostic
*Three determinations (from different samples) produced an 'indeterminate' result because they generated one negative and one positive replicate during the initial run. These ambiguous results were not repeated and omitted from data analysis.

For Intralipid tested at a concentration of 1000 mg/dL, a systemic negative bias was observed when comparing spiked samples to reference samples. A dose-response study was conducted to further characterize potential interference of lipemic samples in the assay. No bias was observed at Intralipid concentration up to 700 mg/dL. The 'Analytical Specificity' section of the Package Insert has been updated to indicate that Intralipid may interfere in the assay at concentrations >700 mg/dL. The 'Specimen Collection and Handling' section of the Package Insert states "*Do not use lipemic or grossly hemolyzed serum samples*".

f. Assay cut-off:

The assay cut-off (index value greater than or equal to 45 is positive) for the KRONUS 21-OHAb ELISA Kit was determined by testing specimens from 1082 healthy blood donors in the United States. Using the 97.5th percentile value (27.4) plus 6 standard deviations, a cut-off value of 45 was deemed appropriate. Utilizing this cut-off value, 1.2% (2/170) of the sera from patients in the Non-Target Disease Group as detailed in the cross-reactivity study presented above in the section on 'Analytical Specificity' were positive for 21-OHAb. Given these results, index values ≥45 are considered positive in the KRONUS 21-OHAb ELISA Kit while samples <45 are considered negative.

2. Comparison studies:

a. Method comparison with predicate device:

Sera from patients diagnosed with Addison's Disease as well as healthy blood donors were tested with both the KRONUS 21-OHAb ELISA Kit and KRONUS 21-OHAb RIA Assay Kit.

Of the 112 Addison's Disease patient sera, 98 (87.5%) were positive by the ELISA assay and 93 (83%) were positive by the RIA assay. The five samples that were positive in the ELISA and negative in the RIA assay were low positive samples with index values of 48.2, 49.1, 66.2, 76.1 and 89.9.

		KRONUS 21-OHAb RIA Assay Kit		
		Positive: > 1 U/mL	Negative: ≤ 1 U/mL	Total
KRONUS 21-OHAb ELISA Kit	Positive: ≥45	93	5	98
	Negative: <45	0	14	14
	Total	93	9	112

Of the 142 healthy blood donors evaluated in both assays, 142 (100%) were negative by the ELISA assay and 141 (99.3%) were negative by the RIA assay.

		KRONUS 21-OHAb RIA Assay Kit		
		Positive: > 1 U/mL	Negative: ≤ 1 U/mL	Total
KRONUS 21-OHAb ELISA Kit	Positive: ≥45	0	0	0
	Negative: <45	1	141	142
	Total	1	141	142

Based on the results of 254 samples evaluated, presented in the table below, the KRONUS 21-OHAb ELISA and KRONUS 21-OHAb RIA Assay have a positive percent agreement of 98.9% (93/94) 95% CI: 94.2%–99.8%, a negative percent agreement of 96.9% (155/160) 95% CI: 92.9%–98.7%, and an overall percent agreement of 97.6% (248/254 samples) 95% CI: 94.9%–98.9%.

		KRONUS 21-OHAb RIA Assay Kit		
		Positive: > 1 U/mL	Negative: ≤ 1 U/mL	Total
KRONUS 21-OHAb ELISA Kit	Positive: ≥45	93	5	98
	Negative: <45	1	155	156
	Total	94	160	254

b. Matrix comparison:

Not applicable. Serum is the only recommended matrix. The Package Insert 'Specimen Collection and Handling'section states "*Serum is the preferred specimen; do not use plasma in the assay*".

3. Clinical studies:

a. Clinical Sensitivity and specificity:

The performance of KRONUS 21-OHAb ELISA Kit was compared to a clinical diagnosis of autoimmune primary adrenal insufficiency. The validation set consisted of clinically characterized sera from 23 patients with isolated Addison's disease, 24 Type I autoimmune polyglandular syndrome (APS), 61 Type II APS and 291 patients with other autoimmune diseases and conditions for autoimmune adrenal disease differential diagnosis for a total of 399 patient serum samples. The results of KRONUS 21-OHAb ELISA Kit for each disease category are shown below:

	# Evaluated	# Positive
Target Disease		
Addison (isolated)	23	18 (78.3%)
Addison PAS Type I	24	18 (75%)
Addison PAS Type II	61	58 (95.1%)
Total		94/108 (87.0%)
Non-Target Disease		
Other Auto-Immune Conditions / Non-infectious Disease		
Rheumatoid Arthritis	16	0 (0.0%)
Type 1 Diabetes	71	2 (2.8%)
Neuromyelitis Optica Spectrum Disorder	8	0 (0.0%)

	# Evaluated	# Positive
Non-Target Disease		
Other Auto-Immune Conditions / Non-infectious Diseases		
Hashimoto's Thyroiditis	30	0 (0.0%)
Graves' Disease	58	0 (0.0%)
Systemic Lupus Erythematosus	9	0 (0.0%)
Amyloidosis	2	0 (0.0%)
Sarcoidosis	14	0 (0.0%)
Vitiligo	4	0 (0.0%)
Sjogren's Syndrome	17	0 (0.0%)
Premature Ovarian Failure	3	0 (0.0%)
Hypoparathyroidism	8	0 (0.0%)
Pernicious Anemia	10	0 (0.0%)
Infectious Diseases		
Coccidiodomycosis	1	0 (0.0%)
Candidiasis	10	0 (0.0%)
Histoplasmosis	10	0 (0.0%)
Mycobacterium Tuberculosis	2	0 (0.0%)
Human Immunodeficiency Virus	10	0 (0.0%)
Cytomeglovirus	3	0 (0.0%)
Post Tuberculosis Addison's Disease	5	0 (0.0%)
	Total	2/291 (0.7%)

Clinical sensitivity and specificity in this sample cohort are summarized in the following table:

		Diagnosis		
		Positive	**Negative**	**Total**
KRONUS 21-OHAb ELISA Kit	Positive: ≥45	94	2	96
	Negative: <45	14	289	303
	Total	108	291	399
Clinical sensitivity: 87.0% (94/108) 95% CI: 79.4% to 92.2% Clinical specificity: 99.3% (289/291) 95% CI: 97.5% to 99.8%				

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

Not applicable

4. Clinical cut-off**:**

   See assay cut-off.

5. Expected values/Reference range:

   The expected values of 21-OHAb were analyzed in accordance with CLSI guideline C28-A3c using 1082 serum samples from apparently healthy blood donors (85% men, 15% women between the age from 11 to 68 years). The mean age of this cohort was 38.3 years (SD of 13.8). The range of index values obtained was 1.9–74.7 with a mean index value of 7.2 (SD of 4.56). The upper limit of the reference range was determined using the non-parametric calculations. The 97.5th percentile value for all samples was 17.1 (90% CI:16.0–22.3). A total of 1080 samples (99.8%) were negative for 21-OHAb and two samples positive for 21-OHAb (0.2%) have index values of 65.7 and 74.7. It is the responsibility of each laboratory to establish its own reference ranges for the population of patients it serves, as expected values are affected by many different factors.

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.