510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k090257

B. Purpose for Submission:
Modification to device

C. Measurand:
Allergen Specific IgE (Cashew, Pistachio, Walnut, Clam, Oyster, Scallop, and Egg)

D. Type of Test:
Quantitative, chemiluminiscent immunoassay

E. Applicant:
Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:
IMMULITE® 2000 3gAllergy™ Specific IgE Assay kit

G. Regulatory Information:

1. Regulation section:
   21 CFR § 866.5750, Radioallergosorbent (RAST) test systems
2. Classification:
   Class II
3. Product code:
   DHB System, Test, Radioallergosorbent (RAST), Immunological
4. Panel:
   Immunology (82)

H. Intended Use:

1. Intended use(s):
   For *in vitro* diagnostic use with the IMMULITE 2000 Analyzer – for the quantitative measurement of allergen-specific IgE in human serum, as an aid in the clinical diagnosis of IgE-mediated allergic disorders.
2. Indication(s) for use:
   Same as Intended use.
3. Special conditions for use statement(s):
   For prescription use only.
4. Special instrument requirements:
   IMMULITE 2000 Analyzer (k970227)

I. Device Description:
Each device contains the following: 3gAllergy™ specific IgE bead pack, alkaline phosphatase conjugated to monoclonal murine anti-human IgE antibody in a human/nonhuman serum buffer matrix, specific IgE adjustors and specific IgE adjustor antibody, ligand-labeled polyclonal goat anti-human IgE antibody with preservative; specific IgE universal kit controls and specific IgE control antibody.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   IMMULITE® 2000 3gAllergy™ Specific IgE
2. Predicate K number(s):
   k013134

3. Comparison with predicates:

Similarities		
Item	New Device	Predicate Device
Intended use	For *in vitro* diagnostic use with the IMMULITE 2000 Analyzer – for the quantitative measurement of allergen-specific IgE in human serum, as an aid in the clinical diagnosis of IgE-mediated allergic disorders.	Same
Technology	Chemiluminescence	Same
Assay performance	Assay to be specific to allergen-specific IgE	Same
Calibrators	Low and high	Same
Controls	Specific IgE Adjustor Antibody, Specific IgE Control Antibody and Specific IgE Universal Kit Controls	Same
Sample type	Serum	Same
Result Interpretation	Quantitative values in kU/L; Interpretation of class results for two scoring systems: Standard and Extended standard: refer to tables attached below.	Same

The Standard classification system utilizes the following class cutoffs:

Class	kU/L	Reactivity for Individual/Component Allergen(s)
0*	< 0.10	Absent or ND[†]
	0.10 – 0.34	Very Low
I	0.35 – 0.69	Low
II	0.70 – 3.49	Moderate
III	3.50 – 17.49	High
IV	17.5 – 52.49	Very High
V	52.5 – 99.99	
VI	≥ 100	

* Class 0 in the standard system signifies: not detectable by second-generation assays.

[†] ND: not detectable by IMMULITE 2000 3gAllergy.

The Extended standard classification system utilizes the following class cutoffs.

Class	kU/L	Reactivity for Individual/Component Allergen(s)
0	< 0.10	Absent or ND[†]
0/1	0.10 – 0.24	Very Low
I	0.25 – 0.39	Low
II	0.40 – 1.29	Moderate
III	1.30 – 3.89	High
IV	3.90–14.99	Very High
V	15.00– 24.99	
VI	≥ 25	

[†] ND: not detectable by IMMULITE 2000 3gAllergy.

The choice of classification systems can be made by the user within the IMMULITE 2000 operational software.
Reference: Hoffman, DR. Comparison of methods of performing the Radioallergosorbent test: Phadebas, Fadal-Nalebuff and Hoffman protocols. Ann Allergy. 1980 Dec; 45(6)

K. Standard/Guidance Document Referenced (if applicable):
Standard documents:
CLSI I/LA 20-A: Evaluation Methods and Analytical Performance Characteristics of Immunological Assays for Human Immunoglobulin E (IgE)
CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Methods; Approved Guideline – Second Edition
Guidance document:
FDA Guidance – Radioallergosorbent Test (RAST) Methods for Allergen-Specific Immunoglobulin E (IgE) 510(k); Final Guidance

L. Test Principle:
The assay is a solid-phase, two-step, chemiluminiscent immunoassay that exploits liquid phase kinetics in a bead format. The allergens are covalently bound to a soluble polymer/co-polymer matrix, which is labeled with a ligand. The assay specific antibody is labeled with alkaline phosphatase. The use of an amino acid co-polymer amplifies the amount of allergen that the matrix can support. The chemiluminiscent detection system is a phosphatase ester of stabilized dioxatane. Cleavage of the phosphate ester by alkaline phosphatase results in the decomposition of dioxatane and the emission of photons, which are quantified by a Luminometer.

M. Performance Characteristics (if/when applicable):
1. Analytical performance:
   a. *Precision/Reproducibility:*
      Reproducibility of the assay was assessed by testing three positive samples and one negative control sample of each allergen(Cashew, Pistachio, Walnut, Clam, Oyster, Scallop, and Egg) in duplicate twice a day for 20 different days (n = 80).
      The sponsor's criterion for the negative sample was the average dose must be

<0.10 kU/L; all negative sample results were within the acceptance criterion. The sponsor's acceptance criterion for the positive samples was ≤15% CV for both within-run and total precision. Three allergen lots were tested for each allergen; representative data from one lot is shown below for the positive samples.

Allergen: Cashew

Sample	Mean (kU/L)	Intra-assay		Inter-assay	
		SD (kU/L)	%CV	SD (kU/L)	%CV
Positive #1	5.20	0.20	3.8	0.27	5.2
Positive #2	9.46	0.42	4.5	0.56	6.0
Positive #3	4.13	0.16	3.9	0.24	5.8

Allergen: Pistachio

Sample	Mean (kU/L)	Intra-assay		Inter-assay	
		SD (kU/L)	%CV	SD (kU/L)	%CV
Positive #1	14.14	0.60	4.2	0.82	5.8
Positive #2	4.33	0.21	4.9	0.28	6.5
Positive #3	1.76	0.08	4.5	0.11	6.0

Allergen: Walnut

Sample	Mean (kU/L)	Intra-assay		Inter-assay	
		SD (kU/L)	%CV	SD (kU/L)	%CV
Positive #1	5.75	0.20	3.5	0.33	5.8
Positive #2	8.72	0.29	3.3	0.44	5.0
Positive #3	2.33	0.09	3.9	0.14	6.1

Allergen: Clam

Sample	Mean (kU/L)	Intra-assay		Inter-assay	
		SD (kU/L)	%CV	SD (kU/L)	%CV
Positive #1	1.43	0.06	4.2	0.08	5.7
Positive #2	4.20	0.16	3.8	0.25	6.0
Positive #3	8.23	0.37	4.5	0.54	6.5

Allergen: Oyster

Sample	Mean (kU/L)	Intra-assay		Inter-assay	
		SD (kU/L)	%CV	SD (kU/L)	%CV
Positive #1	13.18	0.72	5.4	0.92	6.9
Positive #2	0.74	0.03	4.3	0.04	5.7
Positive #3	5.32	0.24	4.6	0.36	6.7

Allergen: Scallop

Sample	Mean (kU/L)	Intra-assay		Inter-assay	
		SD (kU/L)	%CV	SD (kU/L)	%CV
Positive #1	7.16	0.34	4.8	0.42	5.9
Positive #2	3.67	0.17	4.7	0.22	6.0
Positive #3	1.04	0.05	5.2	0.07	6.7

Allergen: Egg

Sample	Mean (kU/L)	Intra-assay		Inter-assay	
		SD (kU/L)	%CV	SD (kU/L)	%CV
Positive #1	10.55	0.50	4.7	0.65	6.1
Positive #2	3.34	0.12	3.6	0.16	4.9
Positive #3	1.99	0.11	5.3	0.13	6.5

Lot to lot reproducibility:
Each of the seven allergens was tested as above with three positive samples
using three different lots (n = 240). Within-run imprecision for the
sample/allergen combinations ranged from 3.9% to 12.1%; total imprecision
of the sample/allergen combinations ranged from 5.1% to 12.5%.

b. *Linearity/assay reportable range:*
Linearity studies:
For each allergen, two samples were diluted in 2-fold serial dilutions to 5
levels. The undiluted (neat) and diluted samples were tested with the specific
allergen to demonstrate linearity at concentrations within the assay limits.
Regression statistics for each allergen comparing observed to expected results
are presented below.

Allergen	Regression Equation	N	Slope	95% CI	Intercept	95% CI
Cashew	y= 1.00x + 0.19	12	1.00	0.98 – 1.02	0.19	- 0.04 – 0.41
Pistachio	y= 1.00x – 0.32	12	1.00	0.99 – 1.02	- 0.32	-0.11 – 0.04
Walnut	y= 1.00x – 0.11	12	1.00	0.99 – 1.02	- 0.11	-0.21 - -0.004
Clam	y= 1.00x + 0.31	12	1.01	0.98 – 1.03	0.31	-0.21 – 0.83
Oyster	y= 1.00x + 0.42	12	1.01	0.97 – 1.05	0.42	-0.26 – 1.10
Scallop	y= 1.00x - 0.02	12	1.00	0.99 – 1.01	- 0.02	-0.17 – 0.13
Egg	y = 1.00x + 0.097	12	1.00	0.99 – 1.01	0.10	-0.04 – 0.23

The assay working range is 0.1 – 100 kU/L.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The calibrators and controls are traceable to the WHO 2nd IRP 75/502
reference standard.

Stability studies:

Accelerated allergen stability testing (15 – 28°C for 57 days; assay kits stored at recommended temperature 2 – 8°C) supports a two-year shelf-life stability claim. Real-time stability testing is underway and currently supports at least a six month shelf-life.

d. *Detection limit:*

Analytical sensitivity: 0.1 kU/L

e. *Analytical specificity:*

Inhibition studies:

Specificity of each allergen was verified through competitive inhibition testing using a single serum sample or pool of sera. A negative sample was used to measure the background response. To initiate the inhibition experiment, 70µL of undiluted and 4 levels of 5-fold serially diluted inhibitor extract were mixed with 250 µL of sample or pool. This mixture was incubated at room temperature (15-28°C) for 1 hour allowing the immunological reaction to occur. Each sample mixture containing the inhibitor extract and the appropriate controls was assayed with 1 lot of each allergen. The percent (%) inhibition was calculated according to the following formula:

$$\left(\frac{\text{(Response of pos. control}_{\text{(pos. sample – neg. sample)}} - \text{sample response with inhibitor extract)}}{\text{(Response of pos. control}_{\text{(pos. sample – neg. sample)}})} \right) \times 100$$

The inhibition study demonstrated that the allergens tested are inhibited by the relevant inhibitor extract in a concentration dependent fashion. Summary inhibition table is presented below.

Cashew			Pistachio			Walnut	
Inhibitor Concentration (mg/mL)	% Inhibition		Inhibitor Concentration (mg/mL)	% Inhibition		Inhibitor Concentration (mg/mL)	% Inhibition
5	100		5	98.8		5	100
1	98.6		1	96.8		1	92.4
0.2	95.1		0.2	89.6		0.2	78.9
0.04	90.3		0.04	76.6		0.04	57.6
0.008	82.9		0.008	71.7		0.008	48.3

Clam			Oyster	
Inhibitor Concentration (mg/mL)	% Inhibition		Inhibitor Concentration (mg/mL)	% Inhibition
5	98.1		5	97.2
1	89.0		1	93.5
0.2	84.0		0.2	84.8
0.04	80.6		0.04	68.4
0.008	77.8		0.008	55.0

Scallop			Egg	
Inhibitor Concentration (mg/mL)	% Inhibition		Inhibitor Concentration (mg/mL)	% Inhibition
5	99.1		5	100
1	96.6		1	100
0.2	91.1		0.2	100
0.04	80.4		0.04	77.4
0.008	69.6		0.008	49.0

Cross-reactivity: The manufacturer states there is no detectable crossreactivity with human serum immunoglobulins IgG, IgA, IgM or IgD at normal physiological levels.

f. Assay cut-off:
Not applicable

2. Comparison studies:
   a. *Method comparison with predicate device:*
   Refer to Clinical studies

3. Clinical studies:
   a. Clinical Sensitivity and specificity
   Clinical performance of Cashew, Pistachio, Walnut, Clam, Oyster, Scallop, and Egg allergens was demonstrated by testing samples from non-atopic and atopic individuals with the IMMULITE® 2000 3gAllergy Specific IgE assay. Atopic patients had documented history of allergy and/or skin-prick testing (positive or negative). Sensitivity and specificity, based on diagnosis of atopic status, are shown in the tables below:

Allergen: Cashew		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	18	0	18
	negative	21	100	121
	Total	39	100	139

		95% CI
Sensitivity:	*46%*	*31 – 62%*
Specificity:	*100%*	*100 - 100%*

7

Allergen: Pistachio		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	23	5	28
	negative	16	116	132
	Total	39	121	160

		95% CI
Sensitivity:	*59%*	*44 – 74%*
Specificity:	*96%*	*92 - 99%*

Allergen: Walnut		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	20	1	21
	negative	19	152	171
	Total	39	153	192

		95% CI
Sensitivity:	*51%*	*36 - 67 %*
Specificity:	*99%*	*98 - 101 %*

Allergen: Clam		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	22	0	22
	negative	20	100	120
	Total	42	100	142

		95% CI
Sensitivity:	*52%*	*37 - 71%*
Specificity:	*100%*	*100 -100%*

Allergen: Oyster		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	24	9	33
	negative	18	107	125
	Total	42	116	158

		95% CI
Sensitivity:	*55%*	*40 - 69%*
Specificity:	*92%*	*87 - 97%*

Allergen: Scallop		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	22	0	22
	negative	20	153	173
	Total	42	153	195

		95% CI
Sensitivity:	*52%*	*37 - 67%*
Specificity:	*100%*	*100 -100%*

Allergen: Egg		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	13	13	26
	negative	5	140	145
	Total	18	153	171

		95% CI
Sensitivity:	*72%*	*52 - 93%*
Specificity:	*92%*	*87 - 96%*

b. Other clinical supportive data (when a. is not applicable):
   Not applicable.
4. Clinical cut-off:
   Not applicable.
5. Expected values/Reference range:
   Not detected.

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.