

**10(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

k081830

B. Purpose for Submission:

New Device

C. Measurand:

Allergen specific IgE (house dust mite, cat, dog, mold, and pollen from common ragweed, Bermuda grass, timothy grass, oak, and elm)

D. Type of Test:

Semi-quantitative lateral flow

E. Applicant:

Phadia AB

F. Proprietary and Established Names:

ImmunoCAP® Rapid System

ImmunoCAP® Rapid Inhalant Profile 1

ImmunoCAP® Rapid Reader

ImmunoCAP® Rapid Reader Check Device

ImmunoCAP® Rapid QC 1

G. Regulatory Information:

1. Regulation section:

21 CFR § 866.5750 Radioallergosorbent (RAST) Immunological Test System

2. Classification:

Class II

3. Product code:

DHB, system, test, radioallergosorbent (RAST) immunological

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

ImmunoCAP® Rapid Inhalant Profile 1, part of the ImmunoCAP Rapid System, is an in vitro semi-quantitative assay for measurement of allergen specific IgE to ten inhalant allergens (house dust mite, cat, dog, mold, and pollen from common ragweed, Bermuda grass, timothy grass, oak, and elm) in heparinized human capillary whole blood, heparinized venous whole blood, or heparinized plasma. It is intended for in vitro diagnostic use as an aid in the clinical diagnosis of IgE mediated allergic disorders in conjunction with other clinical findings, and is to be used in clinical laboratories, licensed under CLIA to perform nonwaived assays.

2. Indication(s) for use:

See intended use above

3. Special conditions for use statement(s):

For professional use only

4. Special instrument requirements:

ImmunoCAP® Rapid Reader

I. Device Description:

The ImmunoCAP® Rapid System is a combination of lateral flow immunoassay reagents and instrument/software for semi-quantitative determination of antibodies or antigens in human capillary whole blood, heparinized venous whole blood or heparinized plasma. It is comprised of the ImmunoCAP® Rapid Inhalant Profile 1 kit (Rapid IP1), ImmunoCAP® Rapid Reader (Rapid Reader), ImmunoCAP® Rapid Reader Check Device (Rapid Reader CD), and ImmunoCAP® Rapid QC1 (Rapid QC1). The Rapid IP1 kit consists of three individually foil wrapped lateral flow devices, each containing 10 allergens coupled with a conjugated gold-anti-IgE (mouse monoclonal) antibody, one 6mL vial Developer Solution, 3 pipettes, and 3 blood sampling devices containing lithium heparin. The Rapid Reader consists of the Rapid Reader instrument and associated software. The Rapid Reader CD and Rapid QC 1 consist of (1 vial each, 0.2 mL positive and negative human plasma controls). The configuration of the allergens on the Rapid IP1 is as follows:

Allergen	Code	flow	Allergen	Code
Cat	e1	↑	Mold (<i>A. alternata</i>)	m6
House dust mite (<i>D. pteronyssinus</i>)	d1		Timothy	g6
Bermuda grass	g2		Elm	t8
Common ragweed	w1		Dog	e5
Oak	t7		House dust mite (<i>D. farinae</i>)	d2

J. Substantial Equivalence Information:

1. Predicate device name(s):
ImmunoCAP Specific IgE
2. Predicate 510(k) number(s):
k962274
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Method	Sandwich immunoassay	Same
Allergens	house dust mite, cat, dog, mold, and pollen from common ragweed, Bermuda grass, timothy grass, oak, and elm	Same
Analyte	Specific IgE	Same

Differences		
Item	Device	Predicate
Intended Use	ImmunoCAP® Rapid Inhalant Profile 1, part of the ImmunoCAP Rapid System, is an in vitro semi-quantitative assay for measurement of	ImmunoCAP Specific IgE Assay is an in vitro quantitative assay for the measurement of allergen specific IgE in human serum

Differences		
Item	Device	Predicate
	allergen specific IgE to ten inhalant allergens (house dust mite, cat, dog, mold, and pollen from common ragweed, Bermuda grass, timothy grass, oak, and elm) in heparinized human capillary whole blood, heparinized venous whole blood, or heparinized plasma. It is intended for in vitro diagnostic use as an aid in the clinical diagnosis of IgE mediated allergic disorders in conjunction with other clinical findings, and is to be used in clinical laboratories, licensed under CLIA to perform nonwaived assays.	or plasma. ImmunoCAP Specific IgE Assay is to be used with the instrument ImmunoCAP 100. It is intended for in vitro diagnostic use as an aid in the clinical diagnosis of IgE mediated allergic disorders in conjunction with other clinical findings, and is to be used in clinical laboratories, as well as physician office laboratories.
Matrix	Capillary whole blood (lithium heparin); Venous whole blood (lithium and sodium heparin); Plasma (sodium heparin),	Serum or Plasma (EDTA, lithium & sodium heparin)
Detection Method	Direct reading	Enzyme-substrate reaction
Technology	Lateral flow	Fluorescence immunoassay
Reaction times	Step 1: 5 minutes Step 2: 15 minutes	Step 1: 30 minutes Step 1: 24 minutes
Detection agent	Anti-human IgE conjugated to gold particles	Anti-human IgE conjugated to beta-galactosidase
Assay Environment	Ambient room conditions (18-32°C, Relative humidity: 15-85%)	Instrument controlled
Sample volume	90 µL: Plasma 110 µL: whole blood (capillary or venous)	40 µL: Plasma or serum
Results Interpretation	Class 1 (Absent or Low) Class 2 (Moderate or High) Class 3 (Very High)	Class 0-1 Class 2-3 Class 4-6

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

Radioallergosorbent Test (RAST) Methods for Allergen-Specific Immunoglobulin E (IgE) 510(k)s; Final Guidance for Industry and FDA
Guidance for the Content of Premarket Submissions for Software Contained in Medical

L. Test Principle:

Rapid IP1 is a lateral flow immunoassay for the semi-quantitative measurement of allergen specific IgE antibodies in human whole blood (WB) or plasma. Ten different allergens are bound to the strips in the Test Windows in separate lines. IgE antibodies present in the patient sample, specific to any of the allergens in the test, bind to the relevant allergen lines on the strips. In a single step, a gold labeled anti-IgE conjugate is solubilized, migrates up the strips and forms a visible red complex with bound IgE antibodies while unbound IgE is washed away. The conjugate continues to migrate, forming visible red lines in the Control Windows. The Rapid Reader quantitatively measures the color saturation and converts the signal into Color Units (CU). The higher the concentration of IgE antibodies in the sample the stronger the color of the red lines, i.e. higher CU values. CU values are then categorized semi-quantitatively into Class 1, 2 or 3.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

ImmunoCAP Rapid IP1 is a unitized point-of care test thus no intra- or within assay run component exists. In the analyses and presentations, the within assay run component is therefore equalized with the between Assay Device component. All precision studies were carried out in accordance to CLSI EP5-A2. For studies using whole blood, total precision was used as the measure of precision. Variation between device, run, lot, and operator were not determined.

Run-to-Run:

Six sensitized single donors and one pooled plasma sample covering the Class 2 and 3 for all the allergens were tested using 3 devices per sample for 20 occasions and 50 sensitized single venous whole blood donor samples covering Classes 1-3 were tested using 3 devices per sample for 4 occasions. A minimum of 4 hours occurred between occasions. For plasma samples, the total variation between Assay Devices, between occasions was estimated to have a CV of 13% and the variation between Assay Devices was 12%, and the variation between occasions 4%. The total variation using venous whole blood from 50 donors assayed in 12 Assay Devices gave a CV of 16%.

Table 1. Coefficients of variance (CV%) for plasma samples tested in 3 Assay Devices on 20 occasions and measured as Color Units.

Allergen	CV% Between Occasions	CV% Between Assay Devices	CV% Total
e1	3.39	10.35	10.89
d1	4.64	13.43	14.21
g2	6.08	14.87	16.06
w1	2.99	13.37	13.70
t7	3.59	11.80	12.33

Allergen	CV% Between Occasions	CV% Between Assay Devices	CV% Total
m6	3.73	12.60	13.14
g6	3.58	9.64	10.28
t8	4.28	11.99	12.73
e5	3.73	13.65	14.15
d2	4.53	11.36	12.23
Total	4.14	12.36	13.04

Table 2. Coefficients of variance (CV%) for venous whole blood from 50 donors assayed in 12 Assay Devices and measured as Color Units.

Allergen	Number of samples	CV% Between Occasions	CV% Between Assay Devices	CV% Total (Sum of components)	CV% Total (All observations)
e1	22	7.25	11.86	13.9	13.55
d1	17	4.89	13.86	14.7	14.55
g2	23	7.86	16.33	18.13	17.82
w1	32	6.89	13.58	15.23	14.94
t7	22	6.5	17.13	18.32	18.11
m6	13	9.68	14.22	17.2	16.7
g6	31	7.3	12.68	14.63	14.3
t8	16	9.7	16.37	19.02	18.57
e5	11	12.01	15.13	19.31	18.62
d2	17	6.09	10.37	12.02	11.74
Total	204	7.68	14.19	16.14	15.8

Lot-to-Lot:

Three manufactured lots were tested using three (3) sensitized single plasma donor and 2 pooled plasma samples, covering Classes 2 & 3 were tested using 8 devices per sample and 50 venous whole blood sample covering Classes 1-3 were tested with 3 devices per sample. For the plasma samples, the total variation between Assay Devices and between lots was estimated to have a CV of 14%, the variation between Assay Devices was 12%, and the variation between lots 7%. The total variation for the venous whole blood samples was 18%CV.

Table 3. Coefficients of variance (CV%) for plasma samples tested in 8 Assay Devices using 3 lots of Assay Devices and measured as Color Units.

Allergen	CV% Between Lots	CV% Between Assay Devices	CV% Total
e1	7.30	12.23	14.24
d1	4.60	10.42	11.40
g2	8.94	13.08	15.85
w1	8.04	10.88	13.53
t7	7.56	12.68	14.76
m6	4.95	17.07	17.78

Allergen	CV% Between Lots	CV% Between Assay Devices	CV% Total
g6	5.97	10.41	12.00
t8	8.92	12.34	15.22
e5	7.77	11.63	13.99
d2	3.96	9.21	10.02
Total	6.99	12.19	14.06

Table 4. Coefficients of variance (CV%) for venous whole blood from 50 donors assayed in 9 Assay Devices (3 Assay Devices from 3 lots) and measured as Color Units.

Allergen	Number of samples	CV% Between Occasions	CV% Between Assay Devices	CV% Total (Sum of components)	CV% Total (All observations)
e1	22	12.17	11.47	16.73	15.58
d1	17	11.56	13.40	17.69	16.72
g2	23	16.95	16.12	23.39	21.80
w1	32	12.67	12.09	17.51	16.33
t7	21	14.80	14.00	20.37	18.98
m6	13	13.11	13.43	18.77	17.59
g6	31	12.70	12.06	17.51	16.32
t8	16	17.62	15.78	23.65	21.95
e5	11	11.92	17.21	20.93	20.07
d2	17	10.04	10.22	14.32	13.42
Total	203	13.56	13.42	19.08	17.84

Site-to-Site:

The site-to-site study was performed using 4 pooled samples from sensitized donors and a single negative sample and were tested using 4 devices per sample for 3 days. The total variation between Assay Devices and between sites was estimated to CV 16%. The variation between Assay Devices was CV 15% and the variation between sites CV 7%.

Table 5. Coefficients of variance (CV%) for plasma samples from sensitized donors tested in 4 Assay Devices at 3 sites and measured as Color Units.

Allergen	CV% Between Sites	CV% Between Assay Devices	CV% Total
e1	6.19	12.16	13.65
d1	5.81	13.15	14.38
g2	6.24	12.31	13.81
w1	3.14	11.01	11.45
t7	7.95	9.02	12.03
m6	6.78	15.54	16.95
g6	7.26	12.21	14.20

Allergen	CV% Between Sites	CV% Between Assay Devices	CV% Total
t8	10.30	18.54	21.21
e5	7.93	23.66	24.95
d2	5.29	11.89	13.01
Total	7.00	14.57	16.17

Operator-to-Operator:

Five venous whole blood samples were tested with five devices per sample with 5 different operators. The total variation between operators was 16%.

Table 6. of variance (CV%) for venous whole blood samples from sensitized donors tested in 5 Assay Devices between 5 different operators and measured as Color Units.

Allergen	Number of samples	CV% Between Occurrences	CV% Between Assay Devices	CV% Total (Sum of components)	CV% Total (All observations)
e1	3	4.31	10.47	11.32	11.19
d1	1	7.48	10.95	13.26	12.90
g2	3	14.86	17.50	22.96	22.14
w1	1	13.73	14.97	20.31	19.52
t7	3	8.10	14.48	16.59	16.26
m6	0	-	-	-	-
g6	3	7.41	15.33	17.03	16.76
t8	0	-	-	-	-
e5	2	5.01	8.86	10.18	9.97
d2	1	10.13	11.68	15.46	14.90
Total	17	9.32	13.76	16.62	16.18

b. Linearity/assay reportable range:

Measuring Range:

The semi-quantitative reportable range is subdivided into Class 1, 2 and 3 which correspond to levels of IgE antibodies spanning the range from Low (0.35 kUA /L) to Very High (100 kUA/L) as measured by ImmunoCAP Specific IgE (IC Specific IgE). A Class 1 result corresponds to absent or low levels, a Class 2 result corresponds to moderate to high levels and a Class 3 result corresponds to very high levels of IgE antibody when compared to IC Specific IgE. In Rapid IP1, the response value (RU) for the class borders between Class 1/2 and Class 2/3 have been established through comparison studies with the IC Specific IgE using samples with known IgE antibody levels.

Linearity:

Four plasma samples from different sensitized donors for each allergen were diluted 4-8 times with IgE negative plasma and tested using one device per sample. The allergen specific IgE antibody level was determined with the IC Specific IgE device.

The linear regression data for each sample are shown in the table below.

Table 7. Linearity study results.

Allergen	Sample	Slope Estimate	95% CI	Intercept Estimate	95% CI	R ²
e1	1	1.10	0.83 – 1.37	0.27	-0.01 – 0.54	0.98
	2	1.06	0.83 – 1.28	0.13	-0.03 – 0.29	1.00
	3	1.14	0.58 – 1.69	0.06	-0.40 – 0.52	0.93
	4	0.86	0.42 – 1.30	-0.78	-1.02 – -0.54	0.93
d1	1	0.96	0.88 – 1.04	-0.25	-0.31 – -0.19	1.00
	2	0.85	0.75 – 0.94	-0.22	-0.29 – -0.15	0.99
	3	0.90	0.73 – 1.07	-0.42	-0.57 – -0.27	0.98
	4	0.92	0.84 – 1.01	-0.35	-0.40 – -0.30	1.00
g2	1	0.78	0.45 – 1.11	-0.75	-0.98 – -0.53	0.95
	2	0.97	0.83 – 1.11	-0.05	-0.17 – 0.06	0.99
	3	0.83	0.60 – 1.06	-0.65	-0.82 – -0.48	0.98
	4	0.71	0.39 – 1.04	-0.78	-1.03 – -0.54	0.94
w1	1	1.19	1.09 – 1.30	-0.58	-0.68 – -0.48	0.99
	2	1.09	0.92 – 1.25	-0.62	-0.74 – -0.51	0.99
	3	1.22	0.98 – 1.46	-1.08	-1.31 – -0.86	0.98
	4	1.13	0.96 – 1.30	-0.47	-0.58 – -0.37	0.99
t7	1	1.02	0.90 – 1.15	-0.56	-0.66 – -0.47	0.99
	2	0.99	0.77 – 1.21	-0.43	-0.59 – -0.27	0.97
	3	1.03	0.66 – 1.41	-1.45	-1.82 – -1.09	0.94
	4	1.15	0.82 – 1.49	-0.64	-0.85 – -0.42	0.96
m6	1	1.27	0.60 – 1.95	-0.43	-0.81 – -0.06	0.92
	2	1.17	0.89 – 1.45	-0.58	-0.71 – -0.46	0.97
	3	1.22	0.89 – 1.56	-0.52	-0.70 – -0.34	0.98
	4	1.16	0.89 – 1.42	-1.13	-1.42 – -0.84	0.98
g6	1	0.91	0.74 – 1.07	-0.45	-0.65 – -0.26	0.99
	2	1.19	1.07 – 1.31	-0.84	-0.94 – -0.75	0.99
	3	1.07	0.59 – 1.55	-0.80	-1.13 – -0.48	0.94
	4	1.12	0.85 – 1.39	-0.65	-0.88 – -0.41	0.98
t8	1	1.15	1.02 – 1.28	-0.71	-0.91 – -0.51	0.99
	2	1.06	0.86 – 1.25	-0.22	-0.38 – -0.06	0.99
	3	1.11	0.68 – 1.55	-0.77	-1.09 – -0.44	0.98
	4	1.11	0.90 – 1.33	-0.82	-0.99 – -0.65	0.99
e5	1	1.08	0.93 – 1.24	-0.06	-0.20 – 0.08	0.99
	2	1.01	0.91 – 1.10	-0.04	-0.12 – 0.04	1.00
	3	0.93	0.73 – 1.14	-0.39	-0.53 – -0.25	0.99
	4	1.30	0.94 – 1.65	-0.18	-0.40 – 0.04	0.98
d2	1	0.92	0.53 – 1.31	-0.27	-0.54 – 0.00	0.95
	2	0.96	0.39 – 1.53	-0.09	-0.65 – 0.46	0.91
	3	0.88	0.58 – 1.18	-0.66	-0.88 – -0.45	0.97
	4	0.93	0.69 – 1.16	-0.27	-0.44 – -0.10	0.98

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

1. Controls:

The ImmunoCAP Rapid QC1 positive and negative controls contain specific IgE antibodies to specified allergens with an assigned response value based on the IC Specific IgE assay values of the candidate raw materials prior to pooling. The final pool of materials is verified by the Rapid IP1. Specific class values for the positive QC1 control, allergens e1, m6, and e5 are Class 3, Class 2, and Class 2, respectively. The response value (RU) for the class borders between Class 1/2 and Class 2/3 have been established through comparison studies with the IC Specific IgE assay using samples with known IgE antibody levels.

2. Stability:

Two positive plasma pools covering all ten allergens and one negative plasma pool were tested with six assay devices per sample and are compared with baseline results. Three lots of Rapid IP1 kit, were placed in reference storage conditions, +2°C to +8°C, for real time stability testing. The testing was performed at start of study, reference condition at 0 months, and after 3, 6, 10, and 13 months. The study is planned to continue until test occasion 25 months. For Lot 1, an initial transport simulation was performed during 1 week. After initial testing at reference conditions, Lot 1 was stored at +32°C. During this week, Lot 1 was also stored at +2°C to +8°C for 18-24 hours at two occasions and at -20°C for 2-3 hours at one occasion. After this week, Lot 1 was returned to reference storage at + 2°C to + 8°C together with Lots 2 and 3.

d. *Detection limit:*

The Limit of Detection (LoD) and Limit of Blank (LoB) were determined using the capillary and venous heparinized whole blood samples obtained from the 245 donors from the Method Comparison study. Plasma was processed from the venous whole blood and the amount of specific IgE antibodies for each of the 10 allergens included in the Rapid IP1 was determined. All results with an allergen specific IgE antibody level lower than 0.1 kU_A/L, i.e. an undetectable level of allergen specific IgE as determined by the IC Specific IgE, was considered as a blank sample for that allergen. The samples fulfilling this criterion were selected for this study. For each sample and allergen, fulfilling the criteria, the Color Units (CU) was recorded. The LoB and LoD were estimated according to CLSI EP17-A. The overall LoB was estimated to 0.16 CU and the LoD to 0.22 CU. The specification for the LoD was within Class I (<0.28 CU). The LoB was calculated according to the following formula: $LoB = \mu_B + 1.645\sigma_B$ and using the 95% percentile: $LoB = Pct_{B\ 100-\alpha}$

The LoD study, using only CU values, gave an estimated overall LoD of CU = 0.22. The Dilution Study (Linearity) gave an estimated level of detection of 0.58kUA/L with a corresponding CU of 0.20. The results for each allergen individually are shown below. Column “LoD Mean CU” is based on LoB using mean and standard deviation, and column “LoD 95% Percentile CU” is based on LoB using the 95% percentile.

Table 8. Limit of Blank values for each individual allergen.

Allergen	No. of Samples	Mean CU	SD (CU)	LoB Mean CU	LoB 95% Percentile CU
e1	179	0.079	0.025	0.119	0.123
d1	206	0.117	0.034	0.173	0.169
g2	172	0.080	0.030	0.130	0.130
w1	137	0.069	0.026	0.111	0.112
t7	13	0.104	0.039	0.169	0.183
m6	121	0.092	0.053	0.178	0.195
g6	148	0.083	0.022	0.118	0.117
t8	210	0.078	0.033	0.131	0.122
e5	147	0.108	0.037	0.168	0.156
d2	207	0.124	0.046	0.200	0.178

Table 9. Limit of Detection values for each individual allergen.

Allergen	LoD Mean CU	LoD 95% Percentile CU
e1	0.150	0.155
d1	0.228	0.223
g2	0.190	0.191
w1	0.165	0.167
t7	0.237	0.256
m6	0.251	0.274
g6	0.161	0.159
t8	0.187	0.174
e5	0.235	0.218
d2	0.246	0.219

e. Analytical specificity:

Plasma and whole blood samples from sensitized and non-sensitized donors were spiked with potentially interfering substances and the studies were performed according CLSI EP-7A2. Samples were distributed in Classes 1, 2 and 3 as measured by ImmunoCAP Rapid IP1. The assay performance of the ImmunoCAP Rapid IP1 for samples both with and without measurable allergen specific IgE antibodies was verified for high levels of total IgE (1,000; 3,000; and 10,000 kU/L). No interference of high levels of total IgE could be observed. The spiking studies regarding potentially interfering substances showed no interference in samples from sensitized and non-sensitized donors samples spiked with hemoglobin (5.5 g/L), heparin (150 IE/mL), bilirubin (340 μ mol/L) and Chyle (1,800 U/mL).

The antibody used for detection in ImmunoCAP Rapid contains the monoclonal (mAb) anti-human IgE antibody clone 390. The specificity of this antibody for human IgE was studied using BIAcore technology. Interactions were studied using polyclonal rabbit anti-mouse-IgG, covalently linked to the reaction surface, to which

the mAb anti-human IgE antibody clone 390 bound upon injection. Subsequent injections were done with purified human myeloma immunoglobulin (Ig) of the IgE, IgG1, IgG2, IgG3, IgG4, IgA, IgM or IgD isotypes. The interactions were studied as measurement of binding and release in comparison with buffer injections and were evaluated in the BIAcore program. As positive control human myeloma IgE (ND) was used and it was injected at the concentrations of 1/1, 1/10, 1/100 and 1/1000 as compared to the other Ig isotypes. No cross reactivity (< 0.1%) with other human immunoglobulin classes

Interference of Total IgE:

Three sets of samples were tested. The first consisted of five sensitized and five non-sensitized single plasma donors, which were each spiked with 1,000 and 3,000 kU/L of IgE; the second set consisted of five sensitized and one non-sensitized single plasma donors, which were spiked to 10,000 kU/L of IgE; and the third set consisted of two sensitized and one non-sensitized single venous whole blood samples, which were spiked to 1,000 kU/L of IgE. Plasma samples were tested with one device per sample and three devices per sample were used for the venous whole blood. All samples were measured in Rapid Reader and the results compared to a non-spiked (neat) sample. The CU value for each plasma sample and the mean CU value for each whole blood sample and allergen were scored as Class 1, Class 2 or Class 3. Results obtained with spiked samples were compared with results obtained with non-spiked samples. The overall agreement was calculated for each spiking level and sample matrix. One plasma sample spiked at 3,000 kU/L and three plasma samples spiked at 10,000 kU/L were discordant when compared to the non-spiked controls. No discordant calls were observed with either plasma or venous whole blood samples spiked with 1,000 kU/L IgE.

Interference of Hemoglobin:

Two sensitized and one non-sensitized samples each for plasma and venous whole blood were spiked with 5.5 g/L hemoglobin and compared to non-spiked samples using three devices per sample. One discordant sample (Class 3) was miscalled (Class 2) with the plasma samples and no discordant samples were seen with the venous whole blood when compared to non-spiked samples. The overall agreement for plasma samples was 97% and 100% for venous whole blood.

Interference of Heparin

Two sensitized and one non-sensitized samples each for plasma and venous whole blood were spiked with 150 IE/mL heparin and compared to non-spiked samples using three devices per sample. No discordant samples were observed for either plasma or whole blood.

Interference of Bilirubin

Two sensitized and one non-sensitized samples each for plasma and venous whole blood were spiked with 340 µmol/L bilirubin and compared to non-spiked samples using three devices per sample. One discordant sample (Class 1) was miscalled (Class 2) with the plasma samples and no discordant samples were seen with the venous whole blood when compared to non-spiked samples. The overall agreement

for plasma samples was 97% and 100% for venous whole blood.

Interference of Chyle

Three sensitized and one non-sensitized plasma samples and two sensitized and one non-sensitized venous whole blood samples were spiked with 1800 U/mL of Chyle and compared to non-spiked samples using three devices per sample. One discordant sample (Class 2) was miscalled (Class 3) with the plasma samples and no discordant samples were seen with the venous whole blood when compared to non-spiked samples. The overall agreement for plasma samples was 97.5% and 100% for venous whole blood.

f. Assay cut-off:

Rapid IP1 gives results in one of three classes of IgE antibody levels, while IC Specific IgE assay reports in one of seven classes. Each of the Rapid IP1 classes, Class 1: absent or low, Class 2: moderate to high, Class 3: very high, encompasses 2 to 3 IC Specific IgE assay classes. As in the IC Specific IgE assay, higher class scores denote increasing levels of specific IgE antibody with the same descriptive terminology for IgE antibody levels. In the IC Specific IgE assay, 0.7 kU_A/L is used as the border between low and moderate and 17.5 kU_A/L is used as the border between high and very high. Rapid IP1 is a rapid, POC, semi quantitative assay with class borders approximated to 1 and 15 kU_A/L respectively. In Rapid IP1, the response value (CU) for the class borders between Class 1 and 2 and Class 2 and 3 have been established through comparison studies with the IC Specific IgE using samples with known IgE antibody levels. A comparison of the measuring range between the Rapid IP1 device, the IC Specific IgE assay, and other reporting methods are depicted in Figure 1, below.

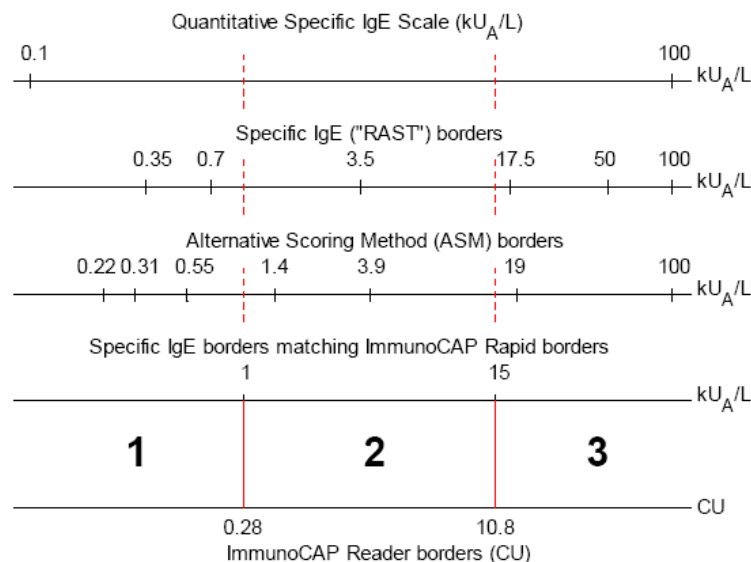


Figure 1. The class scoring range for Rapid IP1 device and corresponding commonly used class scoring and the measuring range for the IC Specific IgE.

2. Comparison studies:

a. *Method comparison with predicate device:*

The comparison study included 245 donors. Heparinized capillary (lithium) and venous (sodium) whole blood were collected from all donors. Plasma was processed from the venous whole blood. All three sample types were used in the Rapid IP1, but plasma was only used with the IC Specific IgE assay. A distribution of allergen levels as determined by the IC Specific IgE assay is depicted in Table 10, below.

Table 10. Distribution of analyte levels for the 245 donors.

Allergen	e1	d1	g2	w1	t7	m6	g6	t8	e5	d2
<1 kUA/L	144	164	152	100	142	188	101	187	171	165
≥1 -<15 kUA/L	77	56	79	88	78	47	90	53	63	49
≥15 kUA/L	24	25	14	57	25	10	54	5	11	31

When compared using a 3x3 format (Table A), the “exact” positive percent agreements (PPA) for Class 2 and Class 3 are indicated by the subscript. The 3x3 format was subsequently collapsed into a 2x2 format (Table B) to calculate the final positive percent (PPA), negative percent (NPA), and overall percent (OA) agreement calculations and is shown below. The NPA is identical between the 3x3 and the corresponding 2x2 comparison tables. The 3x3 tables were collapsed into a 2x2 table based on the following:

		IC Specific IgE				
		Class	3	2	1	
Rapid IP1	3	a	B	c	(+) (+)	(+)
	2	d	e	f		a+b+d+e
	1	g	h	i		c+f
					(-)	(-)
						g+h
						i
						T1+T2
						T3

Tables 11 and 13 below show the semi-quantitative comparison of the Rapid IP1 vs. IC Specific IgE for the different sample types.

11A. Plasma

		IC Specific IgE			Total
		Class	3	2	
Rapid IP1	3	210	17	0	227
	2	46	627	94	767
	1	0	36	1420	1456
Total			256	680	1514
					2450

PPA₃ = 82.03% (210/256)
 PPA₂ = 92.2% (627/680)
 PPA₂₊₃ = 89.4% (837/936)
 OA = 92.1% (2257/2450)

11B. Plasma		IC Specific IgE		
Rapid IP1		(+)	(-)	Total
	(+)	900	94	994
	(-)	36	1420	1456
Total		936	1514	2450

PPA = 96.2% (900/936)
 NPA = 93.8% (1420/1514)
 OA = 94.7% (1320/2450)

12A. Venous WB		IC Specific IgE			
Rapid IP1	Class	3	2	1	Total
	3	202	19	0	221
	2	54	613	97	764
	1	0	48	1417	1465
	Total	256	680	1514	2450

PPA₃ = 82.03% (202/256)
 PPA₂ = 92.2% (613/680)
 PPA₂₊₃ = 89.4% (815/936)
 OA = 92.1% (2257/2450)

12B. Venous WB		IC Specific IgE		
Rapid IP1		(+)	(-)	Total
	(+)	888	97	985
	(-)	48	1417	1465
Total		936	1514	2450

PPA = 94.9% (888/936)
 NPA = 93.6% (1417/1514)
 OA = 94.1% (2305/2450)

13A. Capillary WB		IC Specific IgE			
Rapid IP1	Class	3	2	1	Total
	3	199	18	0	217
	2	57	608	103	768
	1	0	53*	1411	1464
	Total	256	679	1514	2449

*One missing result for capillary whole blood for one allergen due to a blood stain making the result unreadable.

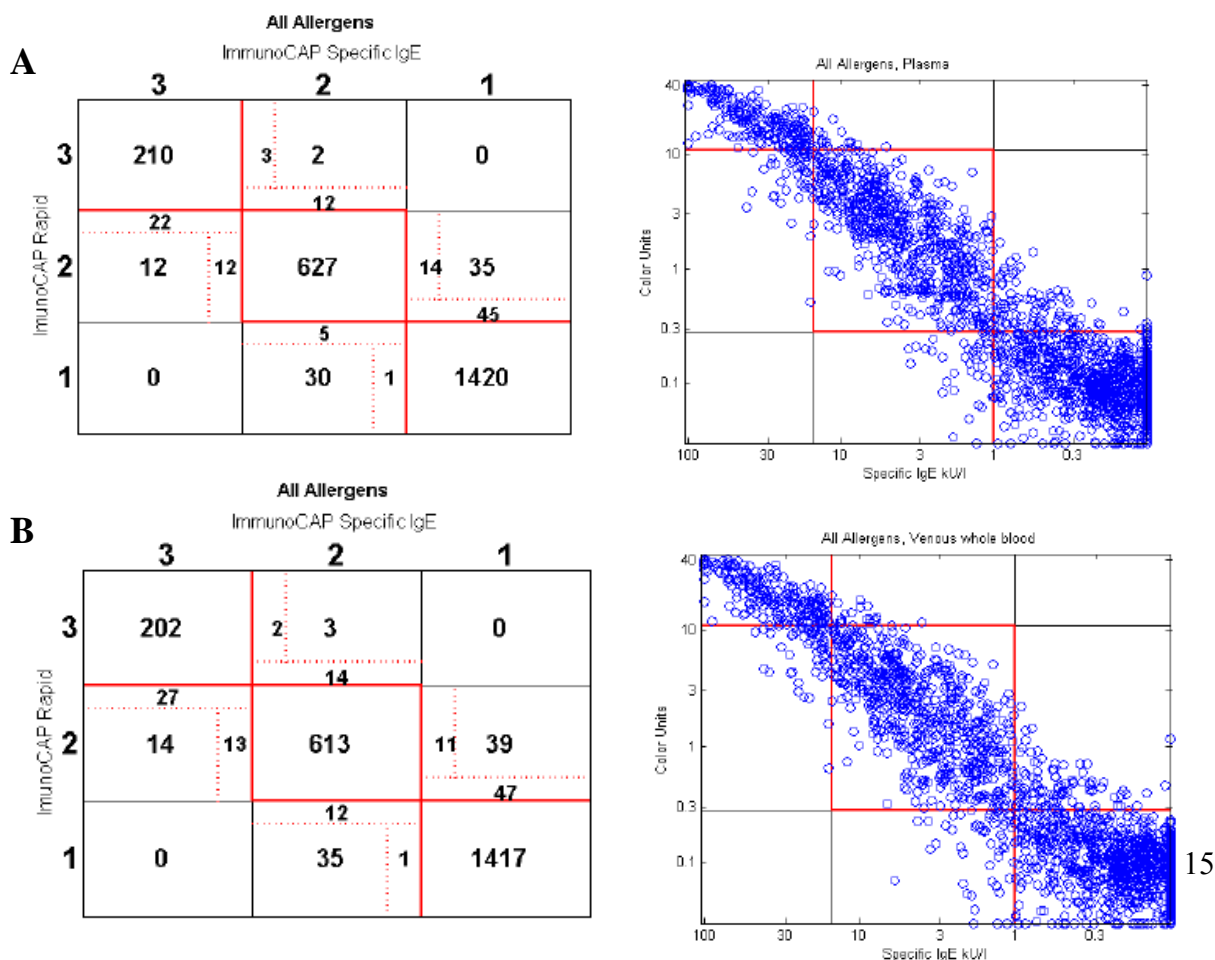
PPA₃ = 77.7% (199/256)
 PPA₂ = 89.5% (608/679)
 PPA₂₊₃ = 86.3% (807/935)
 OA = 90.6% (2218/2449)

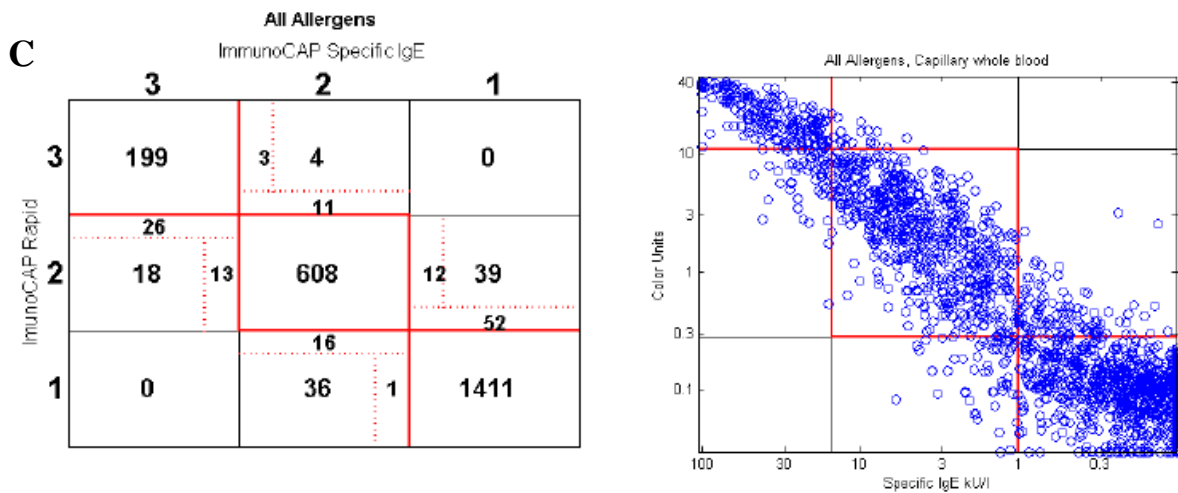
13B. Capillary WB		IC Specific IgE		
		(+)	(-)	
Rapid IP1	(+)	882	103	985
	(-)	53*	1411	1464
		935	1514	2449

PPA = 95.07% (882/935)
 NPA = 93.2% (1411/1514)
 OA = 93.6% (2293/2449)

For the discrepant results for each sample type and allergen, the number of samples at or near the class borders were determined and presented as shown in the example below. A sample falling at or near the border was defined as a sample within a distance of ± 2 SD from the border. The SD used was for the IC Specific IgE assay CV = 10% and for the Rapid IP1 CV = 17% in Class 2 and Class 3, and CV = 30% for samples in Class 1. The figures within the dotted lines are the number of samples at or near the border. The figures in the middle of the different squares are the remaining number samples. The 3x3 tables were also compared to a plot of CU for the Rapid IP1 vs. the quantity of specific IgE as determined by the IC Specific IgE assay for each of the matrices.

Figure 2. Semi-quantitative evaluation with number of samples at or near Class borders for all allergens and CU plot for all allergens for each sample matrix type. A = Plasma, B = venous whole blood, and C = capillary whole blood.





b. Matrix comparison:

The matrix comparison study used blood samples from the Method Comparison study where lithium heparin capillary whole blood and sodium heparin venous whole blood samples were collected. Plasma was processed from the venous whole blood as described above in the “Method comparison to predicate device”. The results for all allergens and matrices showed an overall agreement within Classes was $\geq 91\%$. Capillary and venous whole blood and subsequent processed plasma samples were compared to results of the IC Specific IgE performed on the matched plasma samples and the results are shown in Table 14 and Figure 3, below.

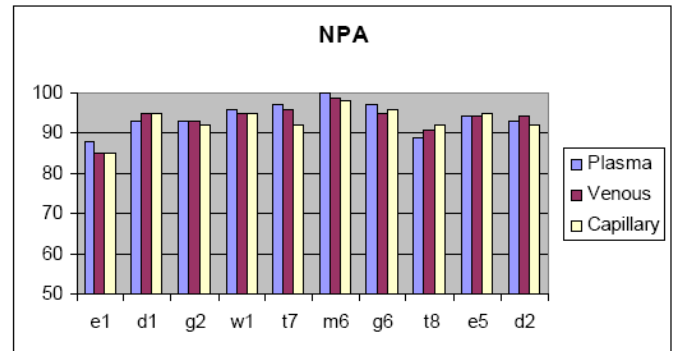
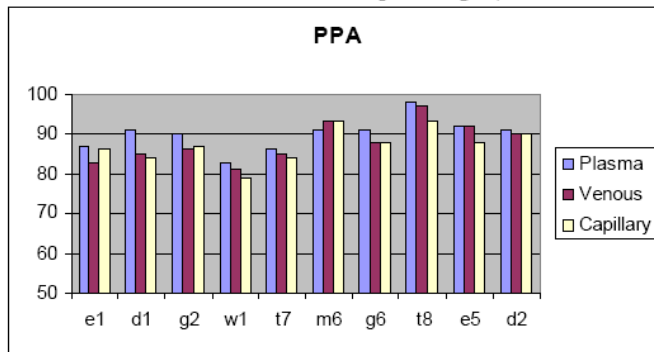
Table 14. Percent Agreements between different matrices by allergen.

Allergen	Number tests	Capillary vs. Venous whole blood			Capillary whole blood vs. Plasma			Venous whole blood vs. Plasma		
		PPA	NPA	OA	PPA	NPA	OA	PPA	NPA	OA
e1	245	96	98	97	92	99	96	93	100	96
d1	245	91	99	96	94	97	96	93	96	95
g2	245	96	99	98	94	98	96	94	97	96
w1	245	90	97	94	91	95	93	95	96	95
t7	245 (244*)	91	96	94*	90	98	94*	93	99	96
m6	245	92	99	97	93	99	98	93	100	98
g6	245	94	96	95	95	96	95	94	97	95
t8	245	96	97	97	99	95	96	99	97	97
e5	245	94	96	95	97	97	97	95	98	97
d2	245	94	100	98	94	98	97	100	98	99
Total	2450 (2449*)			96			96			96

*One missing result for capillary whole blood for one allergen due to a blood stain thus making the result unreadable.

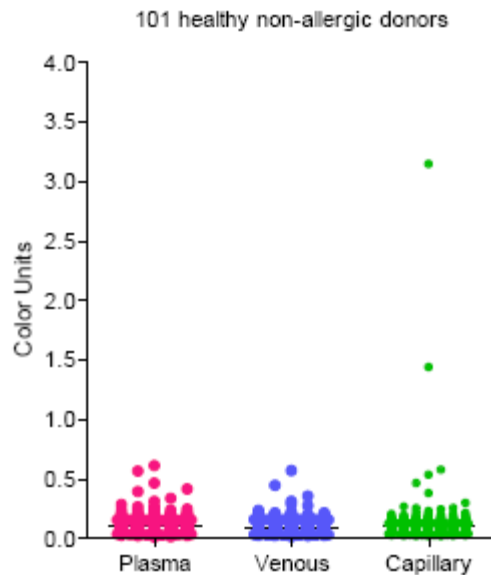
Figure3. Positive and Negative percent agreement comparisons between different

matrices by allergen.



3. Clinical studies:
 - a. *Clinical Sensitivity:*
Not applicable.
 - b. *Clinical specificity:*
Not applicable.
4. Clinical cut-off:
Same as analytical cut-off.
5. Expected values/Reference range:
Matched heparinized capillary (lithium) and heparinized venous whole blood (sodium) samples were obtained from 101 healthy, self-reported, non-allergic donors. Plasma was obtained from the venous whole blood as described in the Method Comparison section, and all sample types were tested on the Rapid IP1 device using one device per sample per matrix. A distribution of color units for the three matrices is shown below.

Figure 5. Distribution of Color Units for 101 self reported, non-allergic donors for three different sample matrices



N. Instrument Name:

ImmunoCAP® Rapid Reader

O. System Descriptions:

1. Device Description:

ImmunoCAP Rapid Reader (Rapid Reader) is a stand alone instrument to be used with ImmunoCAP Rapid Assay Device. The user interface consists of a LCD display with a touch screen and a slot for insertion of the ImmunoCAP Rapid Assay Device.

Assay Device docking system

The slot for the ImmunoCAP Rapid Assay Device has two switches for interaction with the Assay Device.

- One outer switch, to be able to take an image of the Assay Device ID area when inserted into the slot.
- One inner switch; to be able to take a series of images of the Test Window area of the device.

Camera, optics and light source

The color camera has a CCD image sensor with 1024 x 768 pixel resolution, a firewire interface and I/O pins for external signals. The firewire interface delivers the power needed by the camera. A mirror is located between the camera lens and the Assay Device to give a longer optical path and lower optical distortion. Four white color spectrum LED's are placed behind two optical diffusers making the illumination of the Assay Device more even.

Computer system, hard disk and power supply

The computer is a mini-PC (Intel) with 1.67GHz Core2Duo processor, RAM (512MByte) and Hard drive (80GByte). The power supply (65W Input 100-240V ~ 1.6A 50-60 Hz) delivers power to the mini-PC and peripherals.

Display and Touch screen

The display is a LCD panel with 640 x 480 resolution, a standard VGA resolution supported by GNU/Linux operating system. A Touch screen is placed on top of the LCD panel and connected to the mini-PC.

Printer

The printer is a thermo label printer with automatic paper cutter and USB interface.

2. Principles of Operation:

The Reader is part of ImmunoCAP Rapid System, which is a combination of lateral flow immunoassay reagents and instrument/software for semi-quantitative determination of antibodies or antigens in human capillary whole blood, heparinized venous whole blood or heparinized plasma. The ImmunoCAP Rapid Reader quantitatively measures the color saturation and converts the signal into Color Units (CU). The higher the concentration of IgE antibodies in the sample the stronger the color of the red lines, i.e. higher CU values. CU values are then categorized semiquantitatively into Class 1, 2 or 3.

The user performs the Rapid IP1 assay according to the instructions for use and inserts the Rapid IP1 device into the Rapid Reader as shown on the screen of the Reader. If the necessary control conditions are met, assay results will be displayed on the screen. Print the results, by pressing the Print button on the screen. If the Reader does not detect the blood sample or the assay control lines are missing, the Rapid Reader will not report any results. The Reader will display the results as Class 1, 2 or 3.

3. Modes of Operation:

Semi-automated

4. Software:

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

Yes X or No

5. Specimen Identification:

Manual input by user.

6. Specimen Sampling and Handling:

Samples should be obtained and handled according to the laboratory's standard operating procedures and following the protocol described in the package insert for the Rapid IP1 device.

7. Calibration:

The ImmunoCAP Rapid Reader is calibrated at manufacturing and does not require any user calibration.

8. Quality Control:

The user is instructed to perform routine quality control at set schedules which includes cleaning and disinfecting the unit and components. A Reader Check using the Rapid Reader CD is requested by the Rapid Reader the first time the Reader is used during Start-up. Regular Checks will be required every 7 days. A valid Reader Check will reset the 7 day time frame. The operator will be reminded by the Reader at day 5 of the 7 day time frame. A Check button will then appear on the screen, see Figure below. The Reader must register a valid Check within the next 2 days. Note: The Reader will not score any Assay Devices after 7 days have passed, unless a new Check procedure with a valid result has been registered.

The Reader has several internal controls, which automatically check for proper light and optical conditions before reading the test results. If any of these checks fails the Reader will not score Assay Devices. Patient or external control results will not be displayed on the screen if the Reader fails to detect addition of whole blood sample or the development of the control lines in the Control Window of the Assay Device. If this occurs, the Reader flags the assay as invalid and no result will be shown.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

ImmunoCAP Rapid Reader Check Device Stability:

The Rapid Reader CD consists of a plastic housing containing a color card with defined colored areas. The color cards are purchased from an external manufacturer, Scandinavian Colour Institute AB, Stockholm, Sweden. The stability of the color cards are warranted by the Scandinavian Colour Institute AB for a time of 5 years when stored dark in room

temperature. The recommended use of Rapid Reader CD is to remove the Check Device from the foil bag, i.e. stored at reference storage condition, and perform a Reader check once a week. The Scandinavian Colour Institute AB also report an accelerated light stability study where color card samples were exposed to light of high illumination dose, approximately 10 times normal office light, at a temperature of +30°C for 3 months. The conclusion, made by The Scandinavian Colour Institute AB, is that the color cards are stable under these conditions for 50 days. The set stability time of 24 months is based on

- The stability of the color cards is of 5 years when stored dark at room temperature.
- The color cards are stable for 50 days when exposed to a dose of 209184 lx per day.
- According to the recommended use, the reader check device will be exposed to light only for approximately 25 hours (15 minutes at approximately 100 occasions).

ImmunoCAP Rapid Reader Check Device Reproducibility Study:

Three lots of Rapid Reader CDs were measured 52 (lot 1) and 60 (lots 2-3) times each on one instrument. The total variation between Rapid Reader CDs and between lots was CV 0.68%. The variation between Rapid Reader CDs was CV 0.63% and the variation between lots CV 0.25%. The specifications set for between the CDs and between lots was CV <0.7% and a total variation of CD \leq 1%.

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:

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