

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k132801

B. Purpose for Submission:

Addition of seven specific individual allergens to a cleared device (six recombinant and one purified native allergens).

C. Measurand:

Seven new allergen-specific IgE analytes (6 recombinant and 1 native allergen): rBet v 2, (A127 Birch pollen, *Betula verrucosa*); rMal d 1 (A464 Apple, *Malus domestica*); rPru av 1, (A597 Cherry, *Prunus avium*); rPru av 3, (A599 Cherry, *Prunus avium*); rPru av 4 (A600 Cherry, *Prunus avium*); n Pru p 3, (A603 Peach, *Prunus persica*); rMal d 4, (A796 Apple, *Malus domestica*).

D. Type of Test:

Quantitative, chemiluminiscent immunoassay

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

IMMULITE® 2000 3gAllergy™ Specific IgE Universal kit

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):

The IMMULITE 3gAllergy™ Specific IgE Universal kit is 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. The test results are to be used in conjunction with clinical findings and other laboratory tests.

2. Indication(s) for use:

Same as Intended Use

3. Special conditions for use statement(s):

For prescription only

4. Special instrument requirements:

IMMULITE 2000 Analyzer (k970227)

I. Device Description:

Each device contains the following:

- 3gAllergy™ specific IgE bead pack (3 packs of 200 beads coated with anti-ligand)
- Specific IgE reagent wedge: 30 mL alkaline phosphatase (bovine calf intestine) conjugated to monoclonal murine anti-human IgE antibody in a human/nonhuman serum buffer matrix (equally dispensed in 1 wedge with B & C chambers)
- Specific IgE adjustors: low and high (2 vials, 2 mL each) of human IgE in a nonhuman serum matrix with preservative
- Specific IgE adjustor antibody: 2 tubes, 2.75 mL each) ready-to-use ligand-labeled polyclonal goat anti-human IgE antibody with preservative
- Specific IgE universal kit controls: (2 vials, 2 mL each) human IgE in a nonhuman sample matrix with preservative
- Specific IgE control antibody: (2 tubes, 2.75 mL each) ready to use ligand-labeled polyclonal goat anti-human IgE antibody with preservative.

Kit components supplied separately:

- 3gAllergy™ specific IgE sample diluent (concentrated ready to use 1 vial, 25 mL); chemiluminiscent substrate
- Probe wash; probe cleaning kit
- Disposable reaction tubes
- Bar coded allergen holder wedges serially coded 1-33; 34 -66; 67-99
- Allergen tube caps and tube septa.

J. Substantial Equivalence Information:

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

IMMULITE® 2000 3gAllergy™ Specific IgE, k112523

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended use	The IMMULITE 3gAllergy™ Specific IgE Universal kit is for <i>in vitro</i> 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. The test results are to be used in conjunction with clinical findings and other laboratory tests.	Same
Technology	Chemiluminescence	Same
Calibrators	Eight	Same
Controls	Specific IgE and Antibody and Specific IgE Universal Controls	Same
Sample type	Serum	Same
Sample volume	50 µL	Same
Detection Antibody	Monoclonal murine anti-human IgE conjugated to alkaline phosphatase	Same
Process time	65 minutes	Same
Incubation temperature	37°C	Same
Result Interpretation	Quantitative values in kU/L; Interpretation of class results for two scoring systems: Standard and Extended standard	Same

Differences		
Item	Device	Predicate
Total number of Allergens	Seven	Five
Types of Specific Allergens	rBet v 2, (A127 Birch pollen, <i>Betula verrucosa</i>); rMal d 1 (A464 Apple, <i>Malus domestica</i>); rPru av 1, (A597 Cherry, <i>Prunus avium</i>); rPru av 3, (A599 Cherry, <i>Prunus avium</i>); rPru av 4 (A600 Cherry, <i>Prunus avium</i>); n Pru p 3, (A603 Peach, <i>Prunus persica</i>); rMal d 4, (A796 Apple, <i>Malus domestica</i>).	nBet v 1 (A89: Birch Tree), nOle e 1 (A482 : Olive Tree), nArt v 1 (A753: Mugwort weed), Cat Serum Albumin (E220), and Dog Serum Albumin (E221)
Allergen source	Allergenic proteins expressed by recombinant techniques or purified from native sources	Whole allergen extracts or allergenic proteins purified from native sources only

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

CLSI I/LA 20-A2: Analytical Performance Characteristics and Clinical Utility of Immunological Assays for IgE Antibodies

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Methods; Approved Guideline – Second Edition

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limit of Quantitation; Approved Guideline

L. Test Principle:

The assay is a solid-phase, two-step, chemiluminiscent immunoassay that uses 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 four positive samples (with one

sample close to cut-off) and one negative control sample of each allergen: rBet v 2, (A127 Birch pollen); rMal d 1 (A464 Apple); rPru av 1, (A597 Cherry); rPru av 3, (A599 Cherry); rPru av 4 (A600 Cherry); n Pru p 3, (A603 Peach); rMal d 4, (A796 Apple) in duplicate twice a day for 20 different days (n = 80).

The sponsor's acceptance criterion for the negative sample was the average dose level must be <0.10 kU/L; all negative sample mean results were within the acceptance criterion. The positive samples acceptance criterion was $\leq 15\%$ CV for both intra-assay and total precision. All positive sample mean results were within the acceptance criterion. Three allergen lots were tested for each allergen; representative data from one lot is shown below for the positive samples. The intra-assay, inter-assay and total %CV ranges were from 3.09 % to 7.96%; 5.40 % to 11.45%; and 6.80% to 14.60% respectively (see tables below).

rBet v 2, (A127 Birch pollen)

Sample	Mean (kU/L)	Intra-assay		Inter-assay		Total % CV
		SD (kU/L)	%CV	SD (kU/L)	%CV	
Positive #1	0.58	0.02	4.11	0.04	6.53	13.74
Positive #2	1.59	0.06	3.42	0.09	5.75	10.72
Positive #3	7.99	0.28	3.53	0.48	6.04	10.77
Positive #4	0.37	0.03	7.35	0.03	7.45	8.03

rMal d 1 (A464 Apple)

Sample	Mean (kU/L)	Intra-assay		Inter-assay		Total % CV
		SD (kU/L)	%CV	SD (kU/L)	%CV	
Positive #1	0.57	0.03	4.64	0.04	7.47	13.84
Positive #2	2.59	0.11	4.30	0.18	7.04	16.61
Positive #3	5.58	0.23	4.20	0.38	6.76	12.30
Positive #4	0.36	0.03	7.96	0.03	8.67	9.48

rPru av 1, (A597 Cherry)

Sample	Mean (kU/L)	Intra-assay		Inter-assay		Total % CV
		SD (kU/L)	%CV	SD (kU/L)	%CV	
Positive #1	0.61	0.03	5.22	0.05	7.72	10.57
Positive #2	2.48	0.09	3.75	0.25	10.11	11.85
Positive #3	6.97	0.28	3.99	0.47	6.76	13.88
Positive #4	0.38	0.02	6.25	0.03	7.13	14.60

rPru av 3, (A599 Cherry)

Sample	Mean (kU/L)	Intra-assay		Inter-assay		Total % CV
		SD (kU/L)	%CV	SD (kU/L)	%CV	
Positive #1	0.56	0.03	5.04	0.04	6.74	10.32
Positive #2	1.45	0.05	3.45	0.09	5.99	11.28
Positive #3	9.14	0.32	3.50	0.55	6.04	11.18
Positive #4	0.39	0.02	5.74	0.02	6.42	6.80

rPru av 4 (A600 Cherry)

Sample	Mean (kU/L)	Intra-assay		Inter-assay		Total % CV
		SD (kU/L)	%CV	SD (kU/L)	%CV	
Positive #1	0.64	0.02	3.65	0.04	5.91	7.06
Positive #2	1.30	0.04	3.23	0.15	11.45	12.50
Positive #3	8.55	0.34	4.00	0.59	6.88	11.14
Positive #4	0.42	0.03	6.26	0.03	7.06	8.37

n Pru p 3, (A603 Peach)

Sample	Mean (kU/L)	Intra-assay		Inter-assay		Total % CV
		SD (kU/L)	%CV	SD (kU/L)	%CV	
Positive #1	0.58	0.02	3.87	0.04	6.15	8.15
Positive #2	1.64	0.05	3.27	0.10	6.07	7.95*
Positive #3	9.32	0.29	3.09	0.69	7.39	7.80
Positive #4	0.39	0.02	5.52	0.02	6.49	14.03

*Outliers detected on Day 10, Runs 1, 2; Replicates 1, 2 due to operator error;
No outliers used in calculation

rMal d 4, (A796 Apple).

Sample	Mean (kU/L)	Intra-assay		Inter-assay		Total % CV
		SD (kU/L)	%CV	SD (kU/L)	%CV	
Positive #1	0.65	0.02	3.76	0.04	5.58	7.09
Positive #2	1.65	0.05	3.30	0.10	5.79	9.24
Positive #3	7.44	0.24	3.17	0.40	5.40	7.68
Positive #4	0.35	0.03	7.41	0.03	8.56	8.80

Lot to lot imprecision:

The three tested lots were analyzed for lot-to-lot precision using four positive samples (with one sample close to the cut-off) and one negative sample. Between-lot within-run imprecision ranged from 4.43 % to 13.60% and the total imprecision ranged from 5.83 % to 15.75 %. All three lots were within the sponsor's claimed acceptable criterion of $\leq 20\%$ CV.

b. Linearity/assay reportable range:

Linearity studies: For each allergen, two clinical 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 the observed results to expected results of the representative data from first sample are presented below:

Allergen	Regression Equation	Slope 95% CI	Intercept 95% CI	r
rBet v 2	$y = 1.00x + 0.01$	0.95 to 1.05	-0.05 to 0.06	0.998
rMal d 1	$y = 1.01x + 0.09$	0.99 to 1.04	0.002 to 0.18	1.000
rPru av 1	$y = 1.05x + -0.03$	1.01 to 1.08	-0.05 to -0.01	0.999
rPru av 3	$y = 1.00x + 0.05$	0.98 to 1.03	0.02 to 0.07	0.999
rPru av 4	$y = 0.97x + 0.02$	0.94 to 0.99	-0.003 to 0.04	1.000
n Pru p 3	$y = 0.99x + 0.05$	0.96 to 1.02	-0.02 to 0.08	0.999
rMal d 4	$y = 0.96x + 0.04$	0.92 to 1.00	0.01 to 1.00	0.999

The IMMULITE 2000 Calibrator assay range: 0.1 - 100 kU/L.

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

Traceability: The calibrators and controls are traceable to the WHO 2nd IRP 75/502 reference standard for human IgE.

Stability:

Allergen stability: Accelerated allergen stability testing (15-25°C for 60 days at 1, 4, 8, 15, 30, and 60 day intervals; other assay kit components stored at recommended temperature 2-8°C). Testing was performed on three positive samples and one negative sample on two lots. The accelerated study supports a two year shelf-life stability claim. Real-time stability is on-going for all 7 new allergen on three lots with three positive (high: 3.5; moderate 0.7-3.49 and low near the cut-off 0.35-0.69 kU/L) and one negative samples.

On-board/ open-vial stability:

On-board stability testing was performed on three positive samples and one negative sample for 91 days at 2-8°C (at 1, 7, 14, 21, 32, 46, 60, 75 and 90+ day intervals) for each individual specific allergen on three lots. Stability studies support the 90 day on-board stability claim.

Open-vial stability testing was performed on three positive samples and one negative

sample for 180 days at 2-8°C (at 1, 30, 60, 90, 180, and on-going for 360, 390, 540, 720 and 750 day intervals) for each individual specific allergen on three lots. Stability studies support the 180 day on-board stability claim.

d. Detection limit:

Limit of Blank (LoB): Four blank samples (no analyte) were tested in replicates of two, with one run per day, over five days, using two instruments and three lots of allergen. A total of 80 data points were collected for each allergen lot. The Limit of Blank (highest value expected for a sample with no analyte), determined in accordance with CLSI EP17-A, is 0.06kU/L for rPru av 4 (A600 Cherry) and 0.03kU/L for the other six allergens.

Limit of Detection (LoD):

Four low positive samples were tested using 3 allergen lots over 5 days, at one run per day, 2 replicates per run to estimate the LoD. Two instruments were used to collect a total of 60 data points for each new allergen. The Limit of Detection (lowest detectable concentration), determined in accordance with CLSI EP-17-A is ≤ 0.10 kU/L for all seven allergens.

e. Analytical specificity:

(i) Inhibition studies - Related inhibitor

Specificity of each allergen was verified through competitive inhibition testing using a single serum sample or a serum pool. A negative sample was used to measure the background response.

To initiate the inhibition experiment, a minimum of 5 levels of 5-fold diluted inhibitor extract were mixed with sample or pool at a ratio of 1:1 to achieve final inhibitor concentrations of 50 µg/mL and lower. The inhibitor/sample mixtures were 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 were assayed with 1 lot of each allergen. The percent (%) inhibition was calculated according to the following formula:

$$[(C - A/C)] \times 100$$

where:

C = mean response of the positive control (positive sample – negative sample)

A = mean response of sample with inhibitor extract

The data demonstrated that the allergens tested are inhibited by the relevant inhibitor extract in a concentration dependent fashion and are specific for the targeted allergen. The target % inhibition is 50% at the highest inhibitor concentration tested. All seven allergens met the target % inhibition. These results indicate specificity of rBet v 2, (A127 Birch pollen); rMal d 1 (A464 Apple); rPru av 1, (A597 Cherry); rPru av 3, (A599 Cherry); rPru av 4 (A600

Cherry); n Pru p 3, (A603 Peach); rMal d 4, (A796 Apple) allergens.

(ii) Inhibition studies - Unrelated inhibitor

Additional inhibition studies were conducted to show that the specific allergens do not cross-react with unrelated allergens. Three irrelevant allergens, as well as any related components, were included as additional controls. The related components were other components of the parent allergen (if available) or another component from the same group. The final inhibitor concentrations of the additional inhibitors ranged from 500 µg/mL to 1250 µg/mL, determined as 10x the concentration needed to achieve ~100% inhibition on its own allergen device. The same incubation procedure and calculation method were used as described above with relevant inhibitor procedure. The sponsor's acceptance criterion is that the irrelevant allergen controls should demonstrate less than 15% inhibition was met for all seven allergens.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Refer to Clinical studies

b. Matrix comparison:

Not applicable. Serum is the only sample matrix.

3. Clinical studies:

a. Clinical Sensitivity and Specificity:

Clinical performance of the IMMULITE[®] 2000 3gAllergy Specific IgE assay for rBet v 2, (A127 Birch pollen); rMal d 1 (A464 Apple); rPru av 1, (A597 Cherry); rPru av 3, (A599 Cherry); rPru av 4 (A600 Cherry); n Pru p 3, (A603 Peach); rMal d 4, (A796 Apple) allergens was demonstrated by testing samples from non-atopic and atopic individuals.

Atopic patients were selected from patients who had clinical documentation of allergy to specific allergen(s) or allergen group of interest and/or positive skin prick/ scratch test to specific allergen(s) of interest evaluated as 2+ or greater. Information on the skin test allergen extracts (crude or purified) was not documented. Non-atopic patients were clinically known non-allergenic or total IgE <130 ng/mL or 54 IU/mL (2.4 ng = 1 IU).

Comparison to clinical diagnosis was performed on 187 samples for rBet v 2, (A127 Birch pollen); 171 Samples for rMal d 1 (A464 Apple); 154 Samples for rPru av 1, (A597 Cherry); 154 Samples for rPru av 3, (A599 Cherry); 154 Samples for rPru av

4 (A600 Cherry); 155 samples for n Pru p 3, (A603 Peach); and 171 Samples for rMal d 4, (A796 Apple).

Sensitivity and specificity of the new device, based on diagnosis of atopic status, are shown in the tables below (refer to tabulated literature support on allergens with low sensitivity/ low prevalence listed below):

Allergen: rBet v 2, (A127 Birch pollen)		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	25	1	26
	negative	45	116	161
	Total	70	117	187

Sensitivity: 35.7 % (25/70) (95% CI: 24.6 – 48.1%)

Specificity: 99.1 % (116/117) (95% CI: 95.3 – 100%)

Allergen: rMal d 1 (A464 Apple)		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	50	1	51
	negative	4	116	120
	Total	54	117	171

Sensitivity: 92.6% (50/54) (95% CI: 82.1 – 97.9%)

Specificity: 99.1 % (116/1017) (97% CI: 95.3 – 100%)

Allergen: rPru av 1, (A597 Cherry)		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	33	5	38
	negative	4	112	116
	Total	37	117	154

Sensitivity: 89.2% (33/37) (95% CI: 74.6- 97.0%)

Specificity: 95.7 % (112/117) (95% CI: 90.3 – 98.6?%)

Allergen: rPru av 3, (A599 Cherry)		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	10	0	10
	negative	27	117	144
	Total	37	117	154

Sensitivity: 27% (10/37) (95% CI: 13.8 – 44.1%)

Specificity: 100 % (117/117) (95% CI: 96.9 – 100%)

Allergen: rPru av 4 (A600 Cherry)		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	9	1	10
	negative	28	116	144
	Total	37	117	154

Sensitivity: 24.3% (9/37) (95% CI: 11.8 – 41.2%)

Specificity: 99.1 % (116/117) (95% CI: 95.3 – 100%)

Allergen: n Pru p 3, (A603 Peach)		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	11	0	11
	negative	27	117	144
	Total	38	117	155

Sensitivity: 28.9% (11/38) (95% CI: 15.4 – 45.9%)

Specificity: 100 % (117/117) (95% CI: 96.9 – 100%)

Allergen: rMal d 4, (A796 Apple)		Clinical Diagnosis		
		Atopic	Non-atopic	Total
IMMULITE 2000	positive	15	1	16
	negative	39	116	155
	Total	54	117	171

Sensitivity: 27.8% (15/34) (95% CI: 16.5 – 41.6%)

Specificity: 99.1 % (116/117) (95% CI: 95.3 – 100%)

Literature support was provided on allergens with low prevalence and low sensitivity as shown in the Table below:

Specific Allergen % Clinical Sen./Spec.	Literature Citation(s)	Study Used Native or Recombinant Allergen	Prevalence	Reported Sensitivity
A127 (rBet v 2), Birch Pollen 35.7% / 99.1%	Rossi RE, Monasterolo G., Monasterolo S. Detection of specific IgE antibodies in the sera of patients allergic to birch pollen using recombinant allergens Bet v 1, Bet v 2, Bet v 4:evaluation of different IgE reactivity profiles. <i>Allergy</i> . 2003;58(9):929-32.	Native Birch Recombinant Bet v 2	Among patients suffering from pollinosis, 5-54% are sensitive to birch pollen	Among birch-sensitive patients, 45% had serum IgE antibodies to rBet v 2
	Scala E, Alessandri C, Bernardi ML, Ferrara R, Palazzo P, Pomponi D, et al. Cross-sectional survey on immunoglobulin E reactivity in 23077 subjects using an allergenic molecule-based microarray detection system. <i>Clin Exp Allergy</i> . 2010;40(6):911-21.	Recombinant Bet v 2	Among subjects positive to at least one allergenic component, 6% (986/16408) had detectable IgE levels for rBet v 2	(not reported)
	Karamloo F, Schmitz N, Scheurer S et al. Molecular cloning and characterization of a birch pollen minor allergen, Bet v 5, belonging to a family	Recombinant Bet v 2	(not reported)	Among birch-sensitive patients, 10-18% had

Specific Allergen % Clinical Sen./Spec.	Literature Citation(s)	Study Used Native or Recombinant Allergen	Prevalence	Reported Sensitivity
	of isoflavone reductase-related proteins. <i>J Allergy Clin Immunol.</i> 1999;104: 991-9.			serum IgE antibodies to rBet v 2
A599 (rPru av 3), Cherry 27.0% / 100.0%	Eriksson NE, Moller C, Werner S, Magnusson J, Bengtsson U, Zolubas M. Self-reported food hypersensitivity in Sweden, Denmark, Estonia, Lithuania, and Russia. <i>J Investig Allergol Clin Immunol.</i> 2004;14(1):70-9.	Native Cherry	Among 1,139 subjects with food allergies, 19% reported sensitivity to cherry	(not reported)
	Ballmer-Weber B, Scheurer S, Fritsche P, Enrique E, Cistero-Bahima A, Haase T, et al. Component-resolved diagnosis with recombinant allergens in patients with cherry allergy. <i>J Allergy Clin Immunol.</i> 2002; 110(1): 167-73.	Recombinant Pru av 3	(not reported)	Among cherry-sensitive patients, 4% were also sensitized to rPru av 3
A600 (rPru av 4), Cherry 24.3% / 99.1%	Eriksson NE, Moller C, Werner S, Magnusson J, Bengtsson U, Zolubas M. Self-reported food hypersensitivity in Sweden, Denmark, Estonia, Lithuania, and Russia. <i>J Investig Allergol Clin Immunol.</i> 2004;14(1):70-9.	Native Cherry	Among 1,139 subjects with food allergies, 19% reported sensitivity to cherry	(not reported)
	Scheurer S, Pastorello EA, Wangorsch A, Kastner M, Hausteiner D, Vieths S. Recombinant allergens Pru av 1 and Pru av 4 and a newly identified lipid transfer protein in the in vitro diagnosis of cherry allergy. <i>J Allergy Clin Immunol</i> 2001;107(4):724-31.	Recombinant Pru av 4	(not reported)	Among cherry-sensitive patients, 16% had serum IgE antibodies to rPru av 4
	Ballmer-Weber B, Scheurer S, Fritsche P, Enrique E, Cistero-Bahima A, Haase T, et al. Component-resolved diagnosis with recombinant allergens in patients with cherry allergy. <i>J Allergy Clin Immunol.</i> 2002;110(1):167-73.	Recombinant Pru av 4	(not reported)	Among cherry and/or birch sensitive patients, 17-30% were also sensitized to rPru av 4
A603 (nPru p 3), Peach 28.9% / 100%	Eriksson NE, Moller C, Werner S, Magnusson J, Bengtsson U, Zolubas M. Self-reported food hypersensitivity in Sweden, Denmark, Estonia, Lithuania, and Russia. <i>J Investig Allergol Clin Immunol.</i> 2004;14(1):70-9.	Native Peach	Among 1,139 subjects with food allergies, 29% reported sensitivity to peach	(not reported)
	Barber D, de la Torre F, Feo F, Florido F, Guardia P, Moreno C, et al. Understanding patient sensitization profiles in complex pollen areas: a molecular epidemiological study. <i>Allergy.</i> 2008;63: 1550-8.	Recombinant Pru p 3	Among general allergic populations, 13% reported sensitization to rPru p 3	(not reported)
	Caimmi D, Barber D, Hoffmann-Sommergruber K, Amrane H, Bousquet P, Dhivert-Donnadieu H, et al. Understanding the molecular sensitization for Cypress pollen and peach in the Languedoc-Roussillon area. <i>Allergy.</i> 2013; 68: 249-51.	Recombinant Pru p 3	(not reported)	Among 129 patients suffering from rhinitis symptoms, 7% were sensitized to rPru p 3
	Scala E, Alessandri C, Bernardi ML, Ferrara R, Palazzo P, Pomponi D, et al. Cross-sectional survey on immunoglobulin E reactivity in 23077 subjects using an allergenic molecule-based microarray detection system. <i>Clin Exp Allergy.</i> 2010;40(6):911-21.	Native Pru p 3	Among subjects positive to at least one allergenic component, 10% (1607/16408) had detectable IgE levels for nPru p 3	(not reported)
	Barber D, de la Torre F, Lombardero M, Antepara I, Colas C, et al. Component-resolved diagnosis of	Native Pru p 3	Among general allergic	(not reported)

Specific Allergen % Clinical Sen./Spec.	Literature Citation(s)	Study Used Native or Recombinant Allergen	Prevalence	Reported Sensitivity
	pollen allergy based on skin testing with profilin, polcalcin and lipid transfer protein pan-allergens. Clin Exp Allergy. 2009;39:1764-73.		populations, 2-40% reported sensitization to nPru p 3	
	Rodriguez-Perez R, Fernandez-Rivas M, Gonzalez-Mancebo E, Sanchez-Monge R, Diaz-Perales A, Salcedo G. Peach profilin: cloning, heterologous expression and cross-reactivity with Bet v 2. Allergy. 58(7):635-640.	Native Pru p 3	(not reported)	Among peach positive subjects, 4% were also sensitized to nPru p 3
	Fernandez-Rivas M, Gonzalez-Mancebo E, Rodriguez-Perez R, Benito C, Sanchez-Monge R, Salcedo G, et al. Clinically relevant peach allergy is related to peach lipid transfer protein, Pru p 3, in the Spanish population. J Allergy Clin Immunol. 2003;112(4):789-95.	Native Pru p 3	(not reported)	Among peach positive subjects, 62% were also sensitized to nPru p 3
A796 (rMal d 4); Apple 27.8% / 99.1%	Eriksson NE, Moller C, Werner S, Magnusson J, Bengtsson U, Zolubas M. Self-reported food hypersensitivity in Sweden, Denmark, Estonia, Lithuania, and Russia. J Investig Allergol Clin Immunol. 2004;14(1):70-9.	Native Apple	Among 1,139 subjects with food allergies, 45% reported sensitivity to apple	(not reported)
	Barber D, de la Torre F, Lombardero M, Antepara I, Colas C, et al. Component-resolved diagnosis of pollen allergy based on skin testing with profilin, polcalcin and lipid transfer protein pan-allergens. Clin Exp Allergy. 2009; 39: 1764-73.	Recombinant Mal d 4	Among patients suffering from pollinosis, 19% were sensitive to rMal d 4	(not reported)
	Barber D, de la Torre F, Feo F, Florido F, Guardia P, Moreno C, et al. Understanding patient sensitization profiles in complex pollen areas: a molecular epidemiological study. Allergy. 2008;63: 1550-8.	Recombinant Mal d 4	Among patients suffering from pollinosis, 15% were sensitive to rMal d 4	(not reported)
	Fernandez-Rivas M, Bolhaar S, Gonzalez-Mancebo E, Asero R, van LA, Bohle B, Ma Y. Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of allergies to plant foods. J Allergy Clin Immunol. 2006;118(2):481-8.	Recombinant Mal d 4	(not reported)	Among 389 patients with apple allergy, 10-40% were also positive to rMal d 4

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

Not applicable.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

Not detected.

Refer to the Hoffman's 'Standard' and 'Extended Standard' classification system utilizing Class 0 to Class IV cut-offs (see Tables I and II below).

Table-I: 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.

Table-II: 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)

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.