March 23, 2022

Beckman Coulter, Inc.
Veronica Colinayo
Staff Regulatory Affairs
250 S. Kraemer Boulevard, Mail Stop B1.SE.03
Brea, California 92821

Re: K220178
Trade/Device Name: Total Immunoglobulin E (IgE)
Regulation Number: 21 CFR 866.5510
Regulation Name: Immunoglobulins A, G, M, D, And E Immunological Test System
Regulatory Class: Class II
Product Code: DGC
Dated: January 20, 2022
Received: January 21, 2022

Dear Veronica Colinayo:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's

requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Ying Mao. Ph.D.
Chief
Division of Immunology
and Hematology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

Submission Number *(if known)*

K220178

Device Name

Total Immunoglobulin E (IgE)

Indications for Use *(Describe)*

The IgE assay is intended for use in the quantitative determination of Total Immunoglobulin E (IgE) concentration in human serum and plasma (lithium heparin, sodium heparin, K2-EDTA, K3-EDTA) on Beckman Coulter AU/DxC AU clinical chemistry analyzers. The determination aids in the diagnosis of IgE-mediated allergic disorders in conjunction with other clinical findings. For in vitro diagnostic use only.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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1.0 Submitted By

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2.0 Date Submitted

January 20, 2022

3.0 Device Name(s)

3.1 Proprietary Names

Total Immunoglobulin E (IgE)

3.2 Classification Name

Immunoglobulins A, G, M, D, and E immunological test system
[866.5510, Product Code DGC]

4.0 Predicate Device

Candidate Device	Predicate Device	Manufacturer	Docket Number
Total Immunoglobulin E (IgE)	Elecsys IgE II Immunoassay	Roche Diagnostics	K061970

5.0 Device Description

The Total Immunoglobulin E (IgE) reagent kit is in a liquid ready-to-use format designed for optimal performance on Beckman Coulter's AU/DxC AU clinical chemistry analyzers. Each reagent kit contains one buffer reagent (R1), one antibody reagent (R2), and a six-level lot matched calibrator set. The IgE reagent test system utilizes a turbidimetric immunoassay methodology. The AU analyzer measures the change in absorbance at 800 nm to calculate and express the concentration of immunoglobulin E in the test sample based on a stored calibration curve. The IgE assay is traceable to the World Health Organization (WHO) 3rd International Standard 11/234.

6.0 Intended Use

The IgE assay is intended for use in the quantitative determination of Total Immunoglobulin E (IgE) concentration in human serum and plasma (lithium heparin, sodium heparin, K2 EDTA, K3 EDTA) on Beckman Coulter AU/DxC AU clinical chemistry analyzers. The determination aids in the diagnosis of IgE-mediated allergic disorders in conjunction with other clinical findings. For in vitro diagnostic use only.

7.0 Comparison to the Predicate

The following table describes the similarities and differences between the candidate device and the predicate device identified in Section 4.0 of this summary:

Device	Similarities	
Beckman Coulter IgE assay for AU/DxC AU Clinical Chemistry Analyzers	Intended Use: quantitative determination of total IgE for IVD use	Same as Roche's IgE II assay on the Cobas Immunoassay System
	Sample types: serum, plasma (heparin & EDTA)	
	Format: liquid, ready-to-use	
	Antibody: monoclonal, mouse	
	Storage conditions: 2-8°C	
	Differences	
	Operating Principle	IgE: Turbidimetric immunoassay IgE II: Electro-chemiluminescence immunoassay
	Assay Format	IgE: Homogeneous (1 step) IgE II: Heterogeneous (2 step)
	Calibrator scheme	IgE: 6-level multipoint calibration curve IgE II: Barcoded master curve with two-point adjustment
	Calibration Stability	IgE: 14 days IgE II: 7 days
	Traceability	IgE: WHO 3rd IRP 11/234 IgE II: WHO 2nd IRP 75/502
	Analytical Measuring Range	IgE: 20 - 500 IU/mL IgE II: 0.100 - 2500 IU/mL
	Extended Measuring Range (manual or auto-dilution)	IgE: 500 - 1,000 IU/mL IgE II: >2,500 up to 50,000 IU/mL
	Limit of Detection	IgE: 15 IU/mL IgE II: 0.100 IU/mL
	Limit of Quantitation	IGE: 20 IU/mL with ≤ 35% CV IgE II: 0.500 IU/mL with < 20% CV

8.0 Comparison testing

Comparative studies were conducted for the candidate IgE reagent test system on the DxC 700 AU Clinical Chemistry Analyzer. Equivalence was demonstrated through a method comparison study. Additional performance studies verified that the technological differences between the candidate and predicate devices did not adversely affect safety and effectiveness. Discussions of the following performance parameters are presented in this 510(k) Summary:

Method Comparison
Imprecision
Linearity
Sensitivity
Reference Interval
Specificity
Anticoagulants
In-use (Reagent Onboard & Calibration) Stability

9.0 Summary of Performance Data

The data in the Premarket Notification supports a finding of substantial equivalence to measurand test systems already in commercial distribution.

9.1 Method Comparison Summary

Method comparison and bias estimation experiments were designed in accordance with the CLSI Guideline EP09c *"Measurement Procedure Comparison and Bias Estimation Using Patient Samples – Third Edition"*. The study evaluated 136 fresh serum samples spanning the analytical measuring range of the candidate IgE assay, where test sample concentrations ranged from approximately 25 to 499 IU/mL IgE as measured by the predicate assay. The study results are summarized in Table 9.1.1 based on Weighted Deming regression analysis.

Table 9.1.1 IgE Method Comparison Study Summary

Method Y	Slope [95% C.I.]	Intercept (IU/mL) [95% C.I.]	R	N	Method X
Beckman Coulter IgE Assay	0.966 [0.950 – 0.981]	1.0 [-1.0 – 3.0]	0.996	136	Roche Elecsys IgE II Assay

9.2 Precision

Repeatability (within-run) and within-laboratory (total) precision studies were designed from CLSI Guideline EP05-A3 *"Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition"*. Precision studies evaluated three lots of IgE reagent on a single DxC 700 AU analyzer, and one IgE reagent lot on three DxC 700 AU analyzers. Test samples included two levels of human serum-based quality control material and three patient pools. The experimental design used duplicate sample analysis twice daily over twenty working days (N=80) in random order. The performance summary for repeatability (within-run) and total (within-laboratory) imprecision for the candidate IgE assay is provided in Table 9.2.1. The total imprecision estimates include the between-run, between-day, between-lot, and between-instrument components of variance.

Table 9.2.1 IgE Reagent Imprecision Performance Summary

Test Sample	Mean (IU/mL)	Repeatability Results		Criteria*	Total Precision Result		Criteria*	Pass/ Fail
		SD (IU/mL)	%CV		SD (IU/mL)	%CV		
Control 1	113.5	1.9	1.7	≤7.0% CV	2.3	2.0	≤7.5% CV	Pass
Control 2	229.4	2.3	1.0	≤7.0% CV	3.7	1.6	≤7.5% CV	Pass
Pool 1	70.4	2.1	3.0	≤5.0 IU/mL	2.3	3.3	≤7.0 IU/mL	Pass
Pool 2	167.9	2.4	1.4	≤7.0% CV	4.0	2.4	≤7.5% CV	Pass
Pool 3	413.6	3.9	0.9	≤7.0% CV	5.7	1.4	≤7.5% CV	Pass

*Repeatability criteria is 5.0 IU/mL for mean recovery values ≤ 71.4 IU/mL, and 7.0% CV for mean recovery values > 71.4 IU/mL; total precision criteria is 7.0 IU/mL for mean recovery values ≤ 93.3 IU/mL, and 7.5% CV for mean recovery values > 93.3 IU/mL.

9.3 Analytical Range (Linearity)

Analytical range (linearity) studies were designed in accordance with the CLSI guideline EP06-A *"Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline"*. The study used a 15-level linearity test set of inter-diluted patient pools that spanned the claimed analytical measuring range of the candidate IgE assay. The initial assessment of the study data in accordance with the EP06-A document found the modelled non-linearity to be not statistically significant, and the assay was deemed linear; as such, no further evaluation of non-linear models against a bias criterion was required. Table 9.3.1 provides the linearity study summary that supports the analytical measuring range claim for the candidate IgE assay, and Table 9.3.2 provides the linearity test results.

Table 9.3.1 IgE Linearity Study Summary

Sample Type	Acceptance Criterion		Results		Pass/ Fail
	Linear Range (IU/mL)	Allowable Difference Specification	Linear From	Linear To	
Serum	20 – 500	10.0 IU/mL or 10.0%*	13.2	575.5	Pass
Weighted Linear Regression			$y = 1.01273x + 0.630$ $R^2 = 0.99990$		

*Values ≤100 IU/mL use the unit specification, and > 100 IU/mL use the percent specification.

Table 9.3.2 IgE Linearity Study Degree of Non-Linearity Test Results

Sample	Target	Average	Predicted Order 1	Predicted Nonlinear	COV	Bias	Bias Spec	%Bias	%Bias Spec	Pass/ Fail
LIN_01	13.2	13.2	14.0	N/A*	100.0	N/A*	10.0	N/A*	-	Pass
LIN_02	15.1	16.4	15.9	N/A*	100.0	N/A*	10.0	N/A*	-	Pass
LIN_03	24.5	25.2	25.4	N/A*	100.0	N/A*	10.0	N/A*	-	Pass
LIN_04	50.7	52.1	52.0	N/A*	100.0	N/A*	10.0	N/A*	-	Pass
LIN_05	88.2	90.9	90.0	N/A*	100.0	N/A*	10.0	N/A*	-	Pass
LIN_06	155.7	157.6	158.3	N/A*	100.0	N/A*	-	N/A*	10.0	Pass
LIN_07	215.6	220.0	219.0	N/A*	100.0	N/A*	-	N/A*	10.0	Pass
LIN_08	266.2	269.2	270.2	N/A*	100.0	N/A*	-	N/A*	10.0	Pass
LIN_09	331.8	335.3	336.7	N/A*	100.0	N/A*	-	N/A*	10.0	Pass
LIN_10	388.1	392.2	393.7	N/A*	100.0	N/A*	-	N/A*	10.0	Pass
LIN_11	425.6	428.7	431.6	N/A*	100.0	N/A*	-	N/A*	10.0	Pass
LIN_12	463	473.8	469.5	N/A*	100.0	N/A*	-	N/A*	10.0	Pass
LIN_13	511.8	520.9	518.9	N/A*	100.0	N/A*	-	N/A*	10.0	Pass
LIN_14	530.5	542.6	537.9	N/A*	100.0	N/A*	-	N/A*	10.0	Pass
LIN_15	575.5	575.5	583.5	N/A*	100.0	N/A*	-	N/A*	10.0	Pass

*Not Applicable: The non-linearity was deemed not statistically significant, therefore no additional bias assessment between the non-linear and linear models was required.

9.4 Sensitivity (Detection Capability)

Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) studies were designed from the CLSI guideline EP17-A2 "*Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures Approved Guideline - Second Edition*" using the Classical Approach. The EP17 study evaluated two lots of candidate IgE reagent on one DxC 700 AU analyzer. The LoB evaluation assessed four unique lots of Immunoglobulin (Ig)-depleted human serum as the individual blank samples, and the LoD and LoQ evaluations used native patient pools diluted with Ig-depleted serum to achieve the low analyte levels. The results of the Detection Capability Study are shown in Table 9.4.1.

Table 9.4.1 IgE Detection Limit Study Summary (LoB, LoD & LoQ)

Reagent Lot	LoB Result	LoB Claim	LoD Result	LoD Claim	LoQ Result	LoQ Claim	Pass/Fail
	(IU/mL)						
1	5.9	≤10.0	13.8	≤15.0	19.6 at 11.9% CV	≤20.0 at ≤35% CV	Pass
2	7.5		12.5		17.8 at 7.8% CV		Pass

9.5 Reference Interval (Expected values)

IgE reference intervals are significantly influenced by age, sex, geographic location, microflora of the gastrointestinal tract, diet of the population, as well as environmental factors such as climate change.[1] As such, Beckman Coulter recommends that each clinical laboratory establish a range of expected values for its own local population, as dictated by good laboratory practices. The reference intervals presented in Table 7.5.1 were taken from literature.[2]

Table 9.5.1 IgE Expected Values[2]

Analyte	Sample Type	Condition (age)	Levels (kIU/L)*
IgE	Serum	0 - <7 years	<25 – 440
		7 - <19 years	<25 – 450
		Adult (20-60 years)	0 – 160

*Equivalent to IU/mL

[1] CLSI I/LA20, *Analytical Performance Characteristics, Quality Assurance, and Clinical Utility of Immunological Assays for Human Immunoglobulin E Antibodies of Defined Allergen Specificities,* 3rd Edition, October 2016, pp. 23; 27.

[2] Rifai N, *Tietz Handbook of Clinical Chemistry and Molecular Diagnostics*, 6th Ed., Elsevier (2018).

9.6 Analytical Specificity

Interference studies were designed in accordance with the CLSI Guidelines EP07 *"Interference Testing in Clinical Chemistry - Third Edition"* and EP37 *"Supplemental Tables for Interference Testing in Clinical Chemistry"* to identify and evaluate substances that could potentially interfere with the candidate IgE assay. The criteria for no significant interference (NSI) required the test sample (containing interferent) recovery mean to be within ± 10 IU/mL for recovered values ≤ 100 IU/mL, or 10% of the control recovery mean values > 100 IU/mL (sample containing no interferent).

The interference study results are presented in Tables 9.6.1 and 9.6.2. The drug omalizumab is a known interferent with the IgE assay methodology[1] and was not tested; falsely decreased results may occur in patients being treated with the drug. Antibody specificity studies were performed externally by the supplier of the monoclonal antibody component and showed no cross-reactivity with human IgA, IgD, IgG, or IgM.

Table 9.6.1 IgE Endogenous Interferents Study Summary

Substance	Sample Type	Source	Level Tested	Observed Effect
Hemoglobin	Serum	Hemolysate (human)	1,000 mg/dL	NSI
Unconjugated Bilirubin	Serum	Porcine	60 mg/dL	NSI
Lipemia	Serum	Intralipid	1,000 mg/dL	NSI
RF	Serum	Human	250 IU/mL	NSI

NSI = No Significant Interference within ± 10.0 IU/mL or 10%

Table 9.6.2 IgE Common Drug Interferents Study Summary

Substances	Sample Type	Analyte Level (IU/mL)	Range of Observed Mean % Bias	Observed Effect
21 common drugs and concentrations	Serum	~160	-1.6% to 0.9%	NSI

NSI = No Significant Interference within ± 10.0 IU/mL or 10%

[1] Hamilton RG. Accuracy of Food and Drug Administration-cleared IgE antibody assays in the presence of anti-IgE (omalizumab). J Allergy Clin Immunol. 2006;117(4):759-766

9.7 Anticoagulant Studies (Serum vs. Plasma)

Methods comparison studies were used to evaluate plasma as an equivalent sample type. The methods comparison and bias estimation experiments were designed using the CLSI Guideline EP09c *"Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Third Edition"*. The study utilized freshly drawn serum and plasma from apparently healthy adult volunteer donors, where five specimen tubes were drawn from each donor: one serum tube and one tube of each type of anticoagulant. The acceptance criteria and study results are summarized in Table 9.7.1 based on Weighted Deming regression analysis.

Table 9.7.1 IgE Anticoagulant Study Results Summary

Plasma Type	Level Tested	N	Slope [0.9 – 1.1]	Intercept [± 20 IU/mL]	R [≥ 0.97]	Pass/ Fail
Na Heparin	17 Units/mL	55	0.989	0.0	0.999	Pass
Li Heparin	17 Units/mL	55	0.989	-0.5	0.999	Pass
K_2 EDTA	1.8 mg/mL	55	0.986	-1.7	0.997	Pass
K_3 EDTA	1.8 mg/mL	53	0.964	-2.4	0.998	Pass

9.8 In-Use Stability

In-Use Stability studies were designed to verify the open-bottle stability claims for the candidate IgE kit components and the IgE assay calibration interval. Testing was designed in accordance with the CLSI EP25-A guideline "*Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline"* using a classical design for sampling, storage, and testing. The study design evaluated in-use metrics at both the start and end of the shelf stability period for reagent kits stored under normal conditions (2-8°C) and including reagent kits that were exposed to post-shipping stress conditions. Three levels of quality control material were evaluated through the duration of the test period, where the mean IgE recovery at the last time point must be within 10 IU/mL or 10% of the mean Day 0 recovery. Table 9.8.1 summarizes the study results for the pre-stressed reagent kits beyond the claimed shelf life of 24 months.

Table 9.8.1: IgE In-Use Stability Study Summary

Pre-stress Condition	Shelf Life (months)	Stability Parameter (2-8°C storage)	Claim (days)	Tested to (days)	Pass/Fail
Winter	29	Reagent open bottle*	28	29	Pass
Summer					
Winter	29	Calibration interval†	14	15	Pass
Summer					
Winter	29	Calibrator open bottle	45	54	Pass
Summer					

*Reagent stored onboard (on instrument) for study duration

†For Calibration Cycle 1, the Day 15 test point uses the Day 0 calibration curve; for Calibration Cycle 2, the Day 15 test point uses a new calibration curve based on a Day 15 recalibration.

10.0 Conclusion

Beckman Coulter's Total Immunoglobulin E (IgE) Reagent is substantially equivalent to the Roche Elecsys IgE II reagent test system (K061970) as demonstrated through methods comparison and precision studies. The performance testing presented in this submission provides evidence that the device is safe and effective in its intended use.

This 510(k) Summary is being submitted in accordance with the requirements of the Safe Medical Device Act of 1990 and the implementing regulation 21 CFR 807.92.