DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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May 29, 2014

EUROIMMUN US Inc.
c/o Mr. Michael Locke
Director of Regulatory Affairs
1100 The American Road
Morris Plains, New Jersey 07950

Re: K132379
         EUROIMMUN Anti-PLA2R IFA
         Evaluation of Automatic Class III Designation – *De Novo* Request
         Regulation Number: 21 CFR 866.5780
         Regulation Name: Anti-Phospholipase A2 Receptor immunological test system
         Regulatory Classification: Class II
         Product Code: PGV
         Dated: March 26, 2014
         Received: March 28, 2014

Dear Mr. Locke:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration
(FDA) has completed its review of your *de novo* request for classification of the EUROIMMUN
Anti-PLA2R IFA. The intended use of the EUROUMMUN Anti-PLA2R IFA is

> The EUROIMMUN Anti-PLA2R IFA is intended for the qualitative
> determination of IgG class autoantibodies against phospholipase A2 receptor
> (PLA2R) in human serum. It is used as an aid in the diagnosis of primary
> membranous glomerulonephritis (pMGN), in conjunction with other laboratory
> and clinical findings.

FDA concludes that this device, and substantially equivalent devices of this generic type, should be
classified into class II. This order, therefore, classifies the EUROIMMUN Anti-PLA2R IFA, and
substantially equivalent devices of this generic type, into class II under the generic name, "Anti-
Phospholipase A2 Receptor immunological test system".

FDA identifies this generic type of device as: Anti-phospholipase A2 Receptor immunological test
system.

An anti-phospholipase A2 receptor immunological test system is a device that consists of the reagents used to measure by immunochemical techniques the autoantibodies in human blood samples that react with phospholipase A2 receptor. The measurements aid in the diagnosis of primary membranous glomerulonephritis (pMGN), in conjunction with other laboratory and clinical findings.

Section 513(f)(2) of the FD&C Act was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This new law provides two options for *de novo* classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may, within 30 days of receiving notice of the NSE determination, request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the **Federal Register** classifying the device type.

In accordance with section 513(f)(1) of the FD&C Act, FDA issued an order on March 10, 2014 automatically classifying the EUROIMMUN Anti-PLA2R IFA into class III, because it was not within a type of device which was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, nor which was subsequently reclassified into class I or II. On March 28, 2014, FDA filed your *de novo* request for classification of the EUROIMMUN Anti-PLA2R IFA into class II. The petition was submitted under section 513(f)(2) of the FD&C Act. In order to classify the EUROIMMUN Anti-PLA2R IFA into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

After review of the information submitted in the *de novo* request, FDA has determined that the EUROIMMUN Anti-PLA2R IFA intended for use as follows

> The EUROIMMUN Anti-PLA2R IFA is intended for the qualitative determination of IgG class autoantibodies against phospholipase A2 receptor (PLA2R) in human serum. It is used as an aid in the diagnosis of primary membranous glomerulonephritis (pMGN), in conjunction with other laboratory and clinical findings.

can be classified in class II with the establishment of special controls for this type of device. FDA believes that the class II special controls identified later in this order, along with the applicable general controls, provide reasonable assurance of the safety and effectiveness of the device type.

Table – Identified Risks and Required Mitigations

Identified Potential Risks	Required Mitigation Measures
Inaccurate test results that provide false positive and false negative results	Special controls (1), (2), and (3)
Failure to correctly interpret test results can lead to false positive and false negative results	Special controls (1) (iii), (2), and (3)

In addition to the general controls of the FD&C Act, the anti-phospholipase A2 Receptor immunological test system is subject to the following special controls:

    1)   Premarket notification submissions must include the following information:

        i)   A detailed description of the device that includes:

           A)   A detailed description of all components in the test system, including a description of the assay components in the kit and all required ancillary reagents.

           B)   A detailed description of instrumentation and equipment, and illustrations or photographs of non-standard equipment or methods if applicable.

           C)   Detailed documentation of the device software, including, but not limited to, standalone software applications and hardware-based devices that incorporate software where applicable.

           D)   A detailed description of appropriate internal and external quality controls that are recommended or provided. The description must identify those control elements that are incorporated into the recommended testing procedures.

           E)   Detailed specifications for sample collection, processing and storage.

           F)   A detailed description of methodology and assay procedure.

           G)   Detailed specification of the criteria for test results interpretation and reporting.

        ii)   Information that demonstrates the performance characteristics of the device, including:

           A)   Device precision/reproducibility data generated from within-run, between-run, between-day, between-lot, between-operator, between-instruments, between-site, and total precision for multiple nonconsecutive days as applicable. A well characterized panel of patient samples or pools from the intended use population that covers the device measuring range must be used.

           B)   Device linearity data generated from patient samples covering the assay measuring range if applicable.

           C)   Information on traceability to a reference material and description of value assignment of calibrators and controls if applicable.

           D)   Device analytical sensitivity data, including limit of blank, limit of detection and limit of quantitation if applicable.

E)   Device analytical specificity data, including interference by endogenous and exogenous substances, as well as cross-reactivity with samples derived from patients with other autoimmune diseases or conditions.

F)   Device instrument carryover data when applicable.

G)   Device stability data including real-time stability under various storage times and temperatures.

H)   Specimen stability data including stability under various storage times, temperatures, freeze-thaw and transport conditions where appropriate.

I)   Method comparison data generated by comparison of the results obtained with the device to those obtained with a legally marketed predicate device with similar indication of use. Patient samples from the intended use population covering the device measuring range must be used.

J)   Specimen matrix comparison data if more than one specimen type or anticoagulant can be tested with the device. Samples used for comparison must be from patient samples covering the device measuring range.

K)   A description of how the assay cut-off (the medical decision point between positive and negative) was established and validated as well as supporting data.

L)   Clinical performance must be established by comparing data generated by testing samples from the intended use population and differential diagnosis groups with the device to the clinical diagnostic standard. Diagnosis of primary membranous glomerulonephritis must be based primarily on clinical history, physical examination, laboratory tests, including urinalysis, and renal biopsy. Membranous glomerulonephritis is considered to be idiopathic/primary when no secondary cause can be elucidated on the basis of clinical and laboratory criteria. The differential diagnosis groups must include, but not be limited to, secondary membranous glomerulonephritis, membranoproliferative glomerulonephritis, lupus nephritis, focal segmental glomerulosclerosis, IgA nephritis, diabetic nephropathy, systemic lupus erythematosus, systemic sclerosis, and Goodpasture syndrome. Diagnosis of autoimmune and immune-mediated diseases that are associated with membranous glomerulonephritis must be based on established diagnostic criteria and clinical evaluation. For all samples, clinical criteria, including demographic information must be considered in the differentiation between primary membranous glomerulonephritis and secondary membranous glomerulonephritis. The clinical validation results must demonstrate correlation clinical sensitivity and clinical specificity between the test values and the presence or absence of primary membranous glomerulonephritis. The data must be

summarized in tabular format comparing the interpretation of results to the disease status.

M) Expected/ reference values generated by testing an adequate number of samples from apparently healthy normal individuals.

iii) Identification of risk mitigation elements used by the device, including a description of all additional procedures, methods, and practices incorporated into the directions for use that mitigate risks associated with testing.

2) Your 21 CFR 809.10(a) complaint label and 21 CFR 809.10(b) compliant labeling must include warnings relevant to the assay including:
   i) A warning statement that reads "The device is for use by laboratory professionals in a clinical laboratory setting."
   ii) A warning statement that reads "The test is not a stand-alone test but an adjunct to other clinical information. A diagnosis of pMGN or secondary MGN should not be made on a single test result. The clinical symptoms, results on physical examination, and laboratory tests (e.g., serological tests), when appropriate, should always be taken into account when considering the diagnosis of primary versus secondary MGN."
   iii) A warning statement that reads "Absence of circulating PLA2R autoantibody does not rule out a diagnosis of pMGN."
   iv) A warning statement that reads "The assay has not been demonstrated to be effective for monitoring the stage of disease or its response to treatment."
3) Your 21 CFR 809.10(b) complaint must include a description of the protocol and performance studies performed in accordance with special control (1)(ii) and a summary of the results.

In addition, this is a prescription device and must comply with 21 CFR 801.109. Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the anti-phospholipase A2 Receptor immunological test system they intend to market prior to marketing the device and receive clearance to market from FDA.

Please be advised that FDA's decision to grant this *de novo* request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD&C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality

systems (QS) regulation (21 CFR Part 820); and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD&C Act); 21 CFR 1000-1050.

A notice announcing this classification order will be published in the **Federal Register**. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the *de novo* request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

If you have any questions concerning this classification order, please contact Ying Mao at 301-796-6193.

Sincerely yours,

Maria M. Chan -S

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