



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire
Avenue
Document Control Center –
WO66-G609
Silver Spring, MD 20993-0002

April 25, 2016

KRONUS Inc.
Brian Deis
Quality Control and Regulatory Compliance Manager
170 S. Seneca Springs Way, Suite 105
Star, ID 83669

Re: DEN150030
KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay
Evaluation of Automatic Class III Designation – *De Novo* Request
Regulation Number: 21 CFR 866.5665
Regulation Name: Aquaporin-4 autoantibody immunological test system
Regulatory Classification: Class II
Product Code: PNI
Dated: June 30, 2015
Received: July 2, 2015

Dear Mr. Deis:

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 KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay, a prescription device. The KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay is indicated for use as follows:

The KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay is for the semi-quantitative determination of autoantibodies to Aquaporin-4 in human serum. The KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay may be useful as an aid in the diagnosis of Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorders (NMOSD). The KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay is not to be used alone and is to be used in conjunction with other clinical, laboratory, and radiological (e.g., MRI) 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 KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay, and substantially equivalent devices of this generic type, into class II under the generic name, “Aquaporin-4 autoantibody immunological test system.”

FDA identifies this generic type of device as: Aquaporin-4 autoantibody immunological test system.

An Aquaporin-4 autoantibody immunological test system is a device that consists of reagents used to measure by immunochemical techniques autoantibodies in human serum samples that react with Aquaporin-4 (AQP4Ab). The measurements aid in the diagnosis of Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorders (NMOSD) in conjunction with other clinical, laboratory, and radiological (e.g., MRI) findings.

Section 513(f)(2) of the Food, Drug & Cosmetic Act (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 FD&C 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 FD&C 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 FD&C 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.

On July 2, 2015, FDA received your *de novo* request for classification of the KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay. The petition was submitted under section 513(f)(2) of the FD&C Act. In order to classify the KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay 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 KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay indicated for use as follows

The KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay is for the semi-quantitative determination of autoantibodies to Aquaporin-4 in human serum. The KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay may be useful as an aid in the diagnosis of Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorders (NMOSD). The KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay is not to be used alone and is to be used in conjunction with other clinical, laboratory, and radiological (e.g., MRI) 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, including the design controls under 21 CFR part 820, provide reasonable assurance of the safety and effectiveness of the device type.

Table – Identified Risks and Required Mitigations

Identified Risks to Health	Required Mitigations
Inaccurate test results that provide false positive or false negative results can lead to improper patient management	Special controls (1), (2), and (3)
Failure to correctly interpret test results can lead to false positive or false negative results	Special controls (1) (iii), (2), and (3)

In combination with the general controls of the FD&C Act, an Aquaporin-4 autoantibody immunological test system must comply with the following special controls:

- 1) Premarket notification submissions must include the following information:
 - i) A detailed device description including:
 - A) A detailed description of all components including all required ancillary reagents in the test.
 - B) If applicable, a detailed description of instrumentation and equipment, including illustrations or photographs of non-standard equipment or manuals.
 - C) If applicable, detailed documentation of the device software, including, but not limited to, standalone software applications and hardware-based devices that incorporate software.
 - 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 specified testing procedures.
 - E) Detailed specifications for sample collection, processing, and storage.
 - F) A detailed description of methodology and assay procedure.
 - G) 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.
 - H) Detailed specification of the criteria for test results interpretation and reporting.
 - ii) Detailed information demonstrating the performance characteristics of the device, including:
 - A) Device precision/reproducibility data generated from within-run, between-run, between-day, between-lot, between-site, and total precision for multiple nonconsecutive days, as applicable. A well characterized panel of patient samples or pools from the indicated population that covers the device measuring range must be used.
 - B) Device linearity data generated from samples covering the device 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 indications of use. A well-characterized panel of patient samples from the indicated 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 well-characterized patient samples covering the device measuring range.
 - K) Clinical performance must be established by comparing data generated by testing samples from the indicated population and the differential diagnosis or non-target disease groups with the device to the clinical diagnostic standard.
 - (1) The diagnosis of NMO and NMOSD must be based on clinical findings, laboratory tests (e.g., serological tests), and radiological tests (e.g., Magnetic Resonance Imaging).
 - (2) The differential diagnosis or non-target disease group must include the applicable diseases or conditions, including but not be limited to the following: multiple sclerosis, stroke, Lyme disease, shingles, syphilis, human immunodeficiency virus, hepatitis B, tuberculosis, Sjögren's Syndrome, systemic lupus erythematosus, systemic vasculitis, sarcoidosis, Graves' disease, Hashimoto's disease, Type I diabetes, rheumatoid arthritis, Addison's disease, and Myasthenia Gravis.
 - (3) Diagnosis of diseases or conditions for the differential or non-target disease groups must be based on established diagnostic criteria and clinical evaluation.
 - (4) For all samples, the diagnostic clinical criteria and the demographic information must be collected and provided.
 - (5) The clinical validation results must demonstrate clinical sensitivity and clinical specificity for the test values based on the presence or absence of NMO and NMOSD.
 - (6) The data must be summarized in tabular format comparing the interpretation of results to the disease status.
 - L) 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 description of all additional procedures, methods, and practices incorporated into the directions for use that mitigate risks associated with testing.

- 2) The device’s 21 CFR 809.10 (b) compliant labeling must include warnings relevant to the device 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 device is not to be used as a stand-alone device but as an adjunct to other clinical information. A diagnosis of Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorders (NMOSD) should not be made on a single test result. The clinical symptoms, results from physical examination, laboratory tests (e.g., serological tests), and radiological tests (e.g. Magnetic Resonance Imaging), when appropriate, should always be taken into account when considering the diagnosis of NMO and NMOSD.”
- 3) The device’s 21 CFR 809.10(b) compliant labeling must include a detailed 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. 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 Aquaporin-4 autoantibody 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 Parts 801 and 809); 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 Sic Chan by email at Sic.Chan@fda.hhs.gov or by phone at 301-796-7015.

Sincerely yours,

For
Leonthena Carrington, MS, MBA, MT (ASCP)
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostics and Radiological
Health (OIR)
Center for Devices and Radiological Health