



February 21, 2020

Asuragen, Inc.
Bernard Andruss, Ph.D.
Senior Vice President Operations and Regulatory Affairs
2150 Woodward, Suite 100
Austin, Texas 78744

Re: DEN190023

Trade/Device Name: AmplideX Fragile X Dx & Carrier Screen Kit
Regulation Number: 21 CFR 866.5970
Regulation Name: Inherited nucleotide repeat disorder DNA test
Regulatory Class: Class II
Product Code: OYV
Dated: April 17, 2019
Received: April 18, 2019

Dear Bernard Andruss, Ph.D.:

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 AmplideX Fragile X Dx & Carrier Screen Kit, a prescription device, with the following indications for use:

The AmplideX® Fragile X Dx & Carrier Screen Kit is an in vitro diagnostic device that uses polymerase chain reaction (PCR) and capillary electrophoresis to detect and identify the number of cytosine-guanine-guanine (CGG) repeats in the fragile X mental retardation-1 (FMR1) gene using genomic DNA isolated from peripheral whole blood specimens. It is solely intended as an aid in the post-natal diagnosis of fragile X syndrome, and fragile X-associated disorders [i.e., fragile X-associated tremor/ataxia syndrome (FXTAS) or fragile X-associated primary ovarian insufficiency (FXPOI)], and for carrier testing in adults of reproductive age. Assay results are solely intended to be interpreted by healthcare professionals who are board certified in molecular genetics and to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice. Reflex testing, clinical genetic evaluation, and genetic counseling should be offered as appropriate. The test is for use on the 3500Dx Series Genetic Analyzer.

This test is not indicated for use for fetal diagnostic testing, newborn screening or for stand-alone diagnostic purposes.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov. FDA concludes that this device should be classified into Class II. This order, therefore, classifies the AmplideX Fragile X Dx & Carrier Screen Kit, and substantially

equivalent devices of this generic type, into Class II under the generic name Inherited Nucleotide Repeat Disorder DNA test.

FDA identifies this generic type of device as:

Inherited nucleotide repeat disorder DNA test. An inherited nucleotide repeat disorder DNA test is a prescription in vitro diagnostic test that is intended to detect and identify the number of nucleotide repeats in a gene using genomic DNA isolated from post-natal patient specimens. It is solely intended as an aid for carrier testing and as an aid for the diagnosis of inherited nucleotide repeat-associated disorders. Assay results are solely intended to be used in conjunction with other clinical and diagnostic findings. These tests do not include those indicated for use for fetal diagnostic testing or newborn screening.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (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 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 request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. 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 announcing the classification.

On April 18, 2019, FDA received your De Novo requesting classification of the AmpliX Fragile X Dx & Carrier Screen Kit. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the AmpliX Fragile X Dx & Carrier Screen Kit 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, for the previously stated indications for use, the AmpliX Fragile X Dx & Carrier Screen Kit can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Table 1 – Identified Risks to Health and Identified Mitigations

Identified Risks to Health	Mitigation Measures
Incorrect test results	Certain design verification and validation Certain labeling information
Incorrect interpretation of test results	Certain design verification and validation Certain labeling information

In combination with the general controls of the FD&C Act, the inherited nucleotide repeat disorder DNA test is subject to the following special controls:

- (1) The intended use on the device's label required under 21 CFR 809.10(a)(2) and device's labeling required under 21 CFR 809.10(b)(2) must include a:
 - (i) statement that assay results are solely intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, and that reflex testing, clinical genetic evaluation, and genetic counseling should be offered as appropriate.
- (2) The labeling required under 21 CFR 809.10(b) must include:
 - (i) A warning that mosaicism detected in one tissue may not reflect mosaicism in other tissues and that the significance of mosaicism should be interpreted with caution in conjunction with other laboratory and clinical information (e.g., sex of patient, diagnostic testing or carrier screening, patient symptoms) and should include appropriate genetic counseling.
 - (ii) A prominent statement that this test is not indicated for use for fetal diagnostic testing, newborn screening or for stand-alone diagnostic purposes.
 - (iii) Information that addresses how to interpret different result outputs specific to the technology, such as (peaks) in the electropherograms.
- (3) Design verification and validation must include the following:
 - (i) Appropriate design features and control elements incorporated into the testing procedure that mitigate the risk of incorrect clinical results. These include controls as determined acceptable by FDA that:
 - A. Enable the user to determine when the amplification may yield incorrect results,
 - B. Enable the user to determine when cross contamination may have occurred;
 - C. Software risk control measures that address device system hazards; and
 - D. Provide software traceability that ensures all hazards are adequately controlled and that all controls have been validated in the final device design.
 - E. Ensure the instructions for use and test reports appropriately inform the user about the limitations of the assay.
 - (ii) Validated and acceptable, as determined by FDA, criteria for test result interpretation and reporting, including result outputs.
 - (iii) Acceptable, as determined by FDA, evidence demonstrating the clinical validity of the device which supports each indicated diagnostic use, including for each genotype and associated phenotype used in providing a clinical determination for the target population.
 - (iv) Evidence demonstrating acceptable, as determined by FDA, analytical device performance. Patient specimens must represent the full spectrum of expected clinical results and be obtained through unbiased collection. Specimens must be representative of all categories of results and across the range of repeat sizes (e.g., categories and repeat sizes for Fragile X syndrome are: normal 1-44 repeats; intermediate 45-54 repeats; premutation 55 -200 repeats, full mutation greater than 200 repeats), across a range of allelic combinations, be near decision points, and be from both male and female subjects. The number of specimens tested must be sufficient to obtain unbiased estimates of device performance. Analytical validation must include data demonstrating

acceptable, as determined by FDA:

- A. Agreement with a comparator method(s) determined to be acceptable by FDA. This evidence must demonstrate the accuracy for detecting the size of the nucleotide repeats and the diagnostic categorical calls in DNA in the indicated specimen type(s) from patients that are representative of the intended use population. Accuracy must be assessed for both diagnostic and carrier subsets independently.
 - B. Device precision including repeatability and reproducibility, using clinical samples. The study must evaluate all possible sources of variability including, as appropriate, between-site and between operator at a minimum of 3 sites of which 2 must be external with a minimum of 2 operators per site, between-day on a minimum of 3 non-consecutive days, between-run, within-run, between-lot in a minimum of 3 lots, and between instrument on a minimum of 3 instruments. Precision must be demonstrated per specimen and determine for both categorical call and by the size of the repeat (i.e., the percentage of replicates for which the allele fell within the target precision size range). Precision data must be calculated and presented with and without results determined to be invalid.
 - C. Device performance at the limit of detection of each allele across the range of sizes and as a function of the indicated DNA input for the assay.
 - D. Specificity of the reagents for their targets, absence of cross-reactivity, evaluation of sources of interference relevant to the specimen type, and a demonstration of the absence of cross contamination.
 - E. Performance of the pre-analytical methods, including DNA extraction methods.
 - F. Performance of the device across the range of indicated DNA input concentrations for the assay.
 - G. Specimen stability throughout indicated specimen storage ranges, including under expected storage and transport conditions.
- (v) Robust evidence demonstrating that the number and frequency of incorrect results due to mosaicism are clinically acceptable, as determined by FDA.
- (vi) An appropriate traceability plan to minimize the risk of incorrect results over time, including a description of the molecular size standards and other reagents that may be required for result interpretation, as applicable, that demonstrate the reliable interpretation of the size of the fragments.
- (vii) Acceptable, as determined by FDA, device stability protocols and acceptance criteria, that are sufficient to ensure indicated analytical and clinical performance throughout the indicated device stability period. The protocols and acceptance criteria must be adequate to demonstrate that there is no degradation in signal intensity of full mutations when testing a specimen at the latest indicated time point within the indicated device stability that is comprised of the lowest indicated DNA input that can be used.

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 Inherited Nucleotide Repeat Disorder DNA test they intend to market prior to marketing the device.

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 part 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 part 4, subpart A) for combination products; and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD&C Act); 21 CFR parts 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.

For comprehensive regulatory information about medical devices and radiation-emitting products, 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). If you have any questions concerning the contents of the letter, please contact Bowen Cui at 240-402-6148.

Sincerely,

for Reena Philip, Ph.D.
Director
Division of Molecular Genetics and Pathology
OHT7: Office of In Vitro Diagnostics and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health