August 31, 2021

Siemens Healthcare Diagnostics Inc.
Matthew Gee
Sr. Manager, Regulatory Affairs
511 Benedict Ave
Tarrytown, NY 10591

Re: DEN190056
Trade/Device Name: ADVIA Centaur Enhanced Liver Fibrosis (ELF)
Regulation Number: 21 CFR 862.1622
Regulation Name: Prognostic test for assessment of liver related disease progression
Regulatory Class: Class II
Product Code: QQB
Dated: November 3, 2020
Received: November 4, 2020

Dear Matthew Gee:

This letter corrects our previous classification order, dated August 20, 2021, to correct the special controls. The changes are (i) to make a number of minor corrections for grammar and clarity, and (ii) to remove a warning statement not required by the regulation identification.

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 ADVIA Centaur Enhanced Liver Fibrosis (ELF), a prescription device with the following indications for use:

> ADVIA Centaur® Enhanced Liver Fibrosis (ELF™) is for in vitro diagnostic use in the determination of an ELF score based on the combined quantitative measurements of hyaluronic acid, amino-terminal propeptide of type III procollagen, and tissue inhibitor of matrix metalloproteinase 1 in human serum using the ADVIA Centaur XP system.
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> ADVIA Centaur ELF is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to non-alcoholic steatohepatitis (NASH), to assess the likelihood of progression to cirrhosis and liver-related clinical events.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the ADVIA Centaur Enhanced Liver Fibrosis (ELF), and substantially equivalent devices of this generic type, into Class II under the generic name prognostic test for assessment of liver related disease progression.

FDA identifies this generic type of device as:

> **Prognostic test for assessment of liver related disease progression**. A prognostic test for assessment of liver related disease progression is intended to measure one or more analytes obtained from human samples as an aid in assessing progression of liver related disease. This device is not intended for diagnosis of any disease, for monitoring the effect of any therapeutic product, for assessing progression to hepatocellular carcinoma, or for assessing disease progression in individuals with viral hepatitis. It is also not intended for the detection of viruses, viral antigens, or antibodies to viruses.

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 December 26, 2019, FDA received your De Novo requesting classification of the ADVIA Centaur Enhanced Liver Fibrosis (ELF). The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the ADVIA Centaur Enhanced Liver Fibrosis (ELF) 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 and the response to our letter dated March 17, 2020, FDA has determined that, for the previously stated indications for use, the ADVIA Centaur Enhanced Liver Fibrosis (ELF) 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 to health are risks associated with false negative results and false positive results. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Identified Risks to Health	Identified Mitigations
False negative results leading to delayed assessment or treatment	Certain design verification and validation activities, including certain clinical studies Certain labeling information, including certain warnings and performance information
False positive results leading to unnecessary medical procedures	Certain design verification and validation activities, including certain clinical studies Certain labeling information, including certain warnings and performance information

In combination with the general controls of the FD&C Act, a prognostic test for assessment of liver related disease progression is subject to the following special controls:

1. Design verification and validation must include clinical validation data providing:

(i) Information demonstrating clinical performance in a population of patients with liver disease for the different risk categories (e.g., at lower risk, at higher risk) for progression of their disease using well-characterized clinical specimens representing the intended use population collected from multiple intended clinical sites, or an alternative study design determined to be appropriate by FDA.

(ii) Information demonstrating that the outcomes measured and the length of follow-up are clinically relevant for the progression of the specified liver disease.

(iii) Information demonstrating that the clinical criteria for determining whether the target disease is present and that the exclusion and inclusion criteria for subjects, who have the target disease, are appropriate.

(iv) Information demonstrating test performance of the complete test system, including any sample collection and processing steps.

(v) Information, provided or referenced, generated in samples from non-diseased individuals, that demonstrate the upper and lower reference intervals for the output provided by the device.

2. The labeling required under 21 CFR 809.10(b) must include:

(i) A warning statement that test results are not intended to diagnose disease or for monitoring the effect of any therapeutic product.

(ii) A warning statement that test results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including information obtained by alternative methods, and clinical evaluation, as appropriate.

(iii) A warning statement that describes any limitations on the clinical interpretation(s) of the test results.

(iv) Detailed information on device performance, including any limitations to the data generated in the clinical study(ies) and information on device performance in relevant subgroups (e.g., severity of liver disease at the beginning of the observation period) observed in the clinical study(ies).

(v) Information on the analytical performance of the device, including demonstration of reproducibility across multiple sites and multiple reagent lots, or an alternative reproducibility study design determined to be appropriate by FDA.

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.

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 prognostic test for assessment of liver related disease progression 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 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 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.

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 Irene Tebbs at 240-402-0283.

Sincerely,

Kellie B. Kelm -S

Kellie B. Kelm, Ph.D.
Director
Division of Chemistry
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