DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993-0002

SIEMENS HEALTHCARE DIAGNOSTICS, INC.
PHILIP LIU
SENIOR MANAGER, REGULATORY AFFAIRS AND COMPLIANCE
511 BENEDICT AVENUE
TARRYTOWN NY 10591

December 5, 2014

Re: K142758
Trade/Device Name: ADVIA® Centaur HAV Total Assay
Regulation Number: 21 CFR 866.3310
Regulation Name: Hepatitis A virus (HAV) serological assays
Regulatory Class: II
Product Code: LOL
Dated: September 23, 2014
Received: September 25, 2014

Dear Mr. Liu:

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. 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 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 Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. 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 http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Stephen J. Lovell -S for

Sally A. Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of In Vitro Diagnostics
and Radiological Health
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: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
k142758

Device Name
ADVIA Centaur® HAV Total Assay

Indications for Use *(Describe)*

ADVIA Centaur and ADVIA Centaur XP systems:

The ADVIA Centaur HAV Total (HAVT) assay is an in vitro diagnostic immunoassay for the qualitative determination of total antibodies to hepatitis A virus (anti-HAV) in human neonatal, pediatric, and adult serum or plasma (potassium EDTA, lithium or sodium heparinized) using the ADVIA Centaur and ADVIA Centaur XP systems. This anti-HAV assay is indicated as an aid in the diagnosis of previous or ongoing hepatitis A viral infection or in the identification of HAV-susceptible individuals for vaccination.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients.

WARNING: This assay has not been FDA cleared or approved for the screening of blood or plasma donors.

United States federal law restricts this device to sale by or on the order of a physician.

ADVIA Centaur CP system:

The ADVIA Centaur HAV Total (HAVT) assay is an in vitro diagnostic immunoassay for the qualitative determination of total antibodies to hepatitis A virus (anti-HAV) in human neonatal, pediatric, and adult serum or plasma (potassium EDTA, lithium or sodium heparinized) using the ADVIA Centaur CP system. This anti-HAV assay is indicated as an aid in the diagnosis of previous or ongoing hepatitis A viral infection or in the identification of HAV-susceptible individuals for vaccination.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients.

WARNING: This assay has not been FDA cleared or approved for the screening of blood or plasma donors.

United States federal law restricts this device to sale by or on the order of a physician.

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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510(k) Summary for the

ADVIA® Centaur Hepatitis A Total (HAVT) Assay

This 510(k) summary is being submitted in accordance with 21 CFR 807.92.

A. 510(k) Number: k142758

B. Date of Preparation: December 5, 2014

C. Proprietary and Established Names:

ADVIA® Centaur HAV Total Assay

D. Applicant:

Siemens Healthcare Diagnostics Inc.,
511 Benedict Ave, Tarrytown, NY 10591
Philip Liu, Senior Manager, Regulatory Affairs and Compliance
Office: (914) 524-2443
Fax: (914) 524-3579

E. Regulatory Information:

1. Regulation section: 21 CFR § 866.3310
2. Classification: Class II
3. Product Code: LOL, Hepatitis A virus (HAV) serological assays
4. Panel: Microbiology

F. Purpose of this Submission

The purpose of this submission is to add the neonate and pediatric populations to the Intended Use statement of the ADVIA Centaur HAV Total assay approved under PMA P040017.

G. Predicate Device:

The ADVIA® Centaur HAV Total Assay is substantially equivalent to the VITROS Immunodiagnostic Products Anti-HAV Total Reagent Pack cleared under 510(k) k060678.

H. Device Description:

The ADVIA Centaur HAVT reagent kit contains the following:

- ReadyPack® primary reagent pack containing ADVIA Centaur HAVT Lite Reagent, Solid Phase Reagent, and Antigen Reagent
- ReadyPack ancillary pack containing ADVIA Centaur HAVT Ancillary Reagent
- ADVIA Centaur HAVT Low Calibrator
- ADVIA Centaur HAVT High Calibrator
- ADVIA Centaur systems HAVT Master Curve card

- ADVIA Centaur systems HAVT Calibrator Assigned Value Card

The HAVT ReadyPack consists of the following:

Primary reagent pack

- The Lite Reagent is an anti-human HAV monoclonal antibody (~1.0 µg/mL) labeled with acridinium ester and biotinylated monoclonal mouse anti-HAV Fab fragment (~0.08 µg/mL) in phosphate buffer with bovine serum albumin, sodium azide (< 0.1%) and preservatives
- The Solid Phase is a streptavidin coated paramagnetic microparticles in phosphate buffer with bovine serum albumin, sodium azide (< 0.1%) and preservatives
- The Antigen Reagent is HAV antigen (~0.06 µg/mL) in tricine buffer with bovine serum albumin, stabilizers, sodium azide (< 0.1%) and preservatives

Ancillary pack

- The Ancillary Reagent is cysteine in citrate buffer with EDTA and preservatives

HAVT Calibrators

- Processed human plasma positive for anti-HAV antibodies with sodium azide (< 0.1%)

I. Intended Use / Indications for Use:

ADVIA Centaur and ADVIA Centaur XP systems:

The ADVIA Centaur HAV Total (HAVT) assay is an *in vitro* diagnostic immunoassay for the qualitative determination of total antibodies to hepatitis A virus (anti-HAV) in human neonatal, pediatric, and adult serum or plasma (potassium EDTA, lithium or sodium heparinized) using the ADVIA Centaur and ADVIA Centaur XP systems. This anti-HAV assay is indicated as an aid in the diagnosis of previous or ongoing hepatitis A viral infection or in the identification of HAV-susceptible individuals for vaccination.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients.

WARNING: This assay has not been FDA cleared or approved for the screening of blood or plasma donors.

United States federal law restricts this device to sale by or on the order of a physician.

ADVIA Centaur CP system:

The ADVIA Centaur HAV Total (HAVT) assay is an *in vitro* diagnostic immunoassay for the qualitative determination of total antibodies to hepatitis A virus (anti-HAV) in human neonatal, pediatric, and adult serum or plasma (potassium EDTA, lithium or sodium heparinized) using the ADVIA Centaur CP system. This anti-HAV assay is indicated as an aid in the diagnosis of previous or ongoing hepatitis A viral infection or in the identification of HAV-susceptible individuals for vaccination.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients.

WARNING: This assay has not been FDA cleared or approved for the screening of blood or plasma donors.

United States federal law restricts this device to sale by or on the order of a physician.

The assay is also being marketed on the ADVIA Centaur instrument family members, ADVIA Centaur XP and ADVIA Centaur CP, following FDA's *Replacement Reagent and Instrument Family Policy* (December 11, 2003).

J. Substantial Equivalence Information:

Both the ADVIA Centaur HAVT and the VITROS Immunodiagnostic Products Anti-HAV Total Reagent Pack (cleared under 510(k) k060678) employ the prepackaged reagents for use on automated test systems. The Intended Use / Indications for Use, Assay Principle and reagent formulations (use of mouse monoclonal antibodies) are very similar. The major differences between the Device and Predicate Devices are the standardization / traceability and the differences in conjugation of the monoclonal antibodies. A comparison of the important similarities and differences of these assays is shown in the following tables:

Assay:

Similarities:

Item	Modified Device: ADVIA Centaur HAV Total Assay	Predicate Device: VITROS Anti-HAV Total Reagent
Intended Use	For the qualitative determination of total antibodies to hepatitis A virus (anti-HAV) in human neonate, pediatric, and adult samples	For the qualitative detection of total antibody (IgG and IgM) to hepatitis A virus (total anti-HAV) in human adult and pediatric samples
Indications for Use	An aid in the diagnosis of previous or ongoing hepatitis A viral infection or in the identification of HAV-susceptible individuals for vaccination	Aid in the clinical laboratory diagnosis of individuals with acute or past hepatitis A virus infection, or as an aid in the identification of HAV-susceptible individuals prior to HAV vaccination. The detection of HAV-specific antibodies in human serum or plasma is laboratory evidence of acute or recent HAV infection.
Sample type	Serum and Plasma	Same
Measurement	Qualitative	Same
Assay Principle	Competitive immunoassay	Same
Technology	Chemiluminescence	Same

Differences:

Item	Modified Device: ADVIA Centaur HAVT Assay	Predicate Device: VITROS Anti-HAV Total Reagent
Standardization / Traceability	Assay cutoff (Index Value 1.00) is equivalent to 20 mIU/mL standardized to the WHO 2nd International Standard for Anti-Hepatitis A Immunoglobulin (97/646)	Traceable to an in-house reference calibrator which has been value assigned to optimize the clinical sensitivity and specificity performance.
Detection Antibody	Mouse monoclonal anti-HAV antibody labeled with acridinium ester	Mouse monoclonal anti-HAV antibody labeled with horseradish peroxidase (HRP)
Capture Antibody	Fab fragment of mouse monoclonal anti-HAV antibody labeled with biotin	Mouse monoclonal anti-HAV antibody labeled with biotin

K. Standard/Guidance Document Referenced (if applicable):

- None Referenced

L. Test Principle

The ADVIA Centaur HAV Total assay is a fully automated, competitive immunoassay using direct, chemiluminescent technology. The assay consists of three reagent addition and incubation steps. First, the sample is pretreated with Ancillary Reagent containing cysteine. Next, HAV antigen is added from the ancillary well (Antigen Reagent). Lite Reagent and Solid Phase are then added. The Lite Reagent contains monoclonal mouse antibody to HAV antigen labeled with acridinium ester and biotinylated Fab fragment of a monoclonal mouse antibody to HAV antigen. The Solid Phase contains streptavidin covalently coupled to paramagnetic particles. After the final incubation, the immuno-complex formed is washed with Wash 1 prior to initiation of the chemiluminescent reaction.

M. Performance Characteristics

The following studies were performed to demonstrate that the neonate and pediatric populations can be used in the ADVIA Centaur HAV Total assay:

- **Spike / recovery of anti-HAV antibodies into neonate samples**

A study was conducted to evaluate the results observed when neonatal samples are tested with the ADVIA Centaur HAVT assay. Cord blood serum was used as a surrogate for neonatal serum. A total of thirty (30) cord blood and 30 adult serum samples were spiked with anti-HAV positive stock to yield samples at different analyte levels. The distribution of percent bias between the index values of the cord blood serum samples and the mean observed index values of the adult serum samples are summarized in the following table:

Distribution of %Bias (Neonatal Cord Blood vs. Adult Serum)

Adult Spiked Observed Mean (Index)	Number Tested (n)	Distribution of % Bias			
		≤ 10%	> 10% to ≤ 20%	> 20% to ≤ 30%	> 30%
Negative (0.6)	6	0.0% (0/6)	33.3% (2/6)	33.3% (2/6)	33.3% (2/6)
Cut-off (1.0)	6	16.7% (1/6)	33.3% (2/6)	50.0% (3/6)	0.0% (0/6)
Low Pos. (1.7)	12	83.3% (10/12)	16.7% (2/12)	0.0% (0/12)	0.0% (0/12)
High Pos. (5.8)	6	83.3% (5/6)	16.7% (1/6)	0.0% (0/6)	0.0% (0/6)
Total:	30	53.33% (16/30)	23.33% (7/30)	16.67% (5/30)	6.67% (2/30)

- **Spike / recovery of anti-HAV antibodies into pediatric samples**

A study was conducted to evaluate the results observed when pediatric samples are tested with the ADVIA Centaur HAVT assay. A total of thirty (30) pediatric and 30 adult serum samples were spiked at different analyte levels. The distribution of percent bias between the index values of the spiked pediatric serum samples and the mean observed index values of the adult serum samples are summarized in the following table:

Distribution of %Bias (Pediatric vs. Adult Serum)

Adult Spiked Observed Mean (Index)	Number Tested (n)	Distribution of % Bias			
		≤ 10%	> 10% to ≤ 20%	> 20% to ≤ 30%	> 30%
Negative (0.6)	6	0.0% (0/6)	0.0% (0/6)	0.0% (0/6)	100.0% (6/6)
Cut-off (1.0)	6	66.7% (4/6)	16.7% (1/6)	16.7% (1/6)	0.0% (0/6)
Low Pos. (1.7)	12	50.0% (6/12)	41.7% (5/12)	0.0% (0/12)	8.3% (1/12)
High Pos. (5.8)	6	83.3% (5/6)	16.7% (1/6)	0.0% (0/6)	0.0% (0/6)
Total:	30	50% (15/30)	23.33% (7/30)	3.33% (1/30)	23.33% (7/30)

- **Concordance Study using Pediatric Samples (Clinical)**

Fifty-five (55) pediatric serum samples (male and female, age range from 2 to 21 years), including samples from a high risk population, were evaluated with the ADVIA Centaur HAVT assay and another commercially available assay. The percent agreement between the assays is shown as follows:

Results of Pediatric Population (2 - 21 years) Comparison Study

		Comparative anti-HAV Total Assay			
		Positive	Borderline	Negative	Totals
ADVIA Centaur anti-HAV Total Assay	Reactive	11	0	1	12
	Nonreactive	0	2	41	43
	Total	11	2	42	55

% Positive Agreement = 84.62% (11/13*)

95% Confidence Interval = 54.55 to 98.08%

% Negative Agreement = 97.62% (41/42)

95% Confidence Interval = 87.43 to 99.94%

* The 2 borderline results from the comparative assay are scored as discordant results in the %Positive Agreement calculation. The ADVIA Centaur HAVT assay does not have a borderline or an equivocal zone.

The inclusion of neonate and pediatric populations in the ADVIA Centaur HAVT intended use does not necessitate the collection of additional analytical performance data since there was no change to the assay. All performance data are cross-referenced to the original Premarket Approval for the ADVIA Centaur HAVT assay on the ADVIA Centaur systems (P040017).

Specifically, the following studies are not needed for the purpose of this submission:

- Precision/Reproducibility
- Calibrator/Assay Traceability
- Calibrator/Assay Stability
- Assay Cut-off
- Method Comparison
- Matrix Comparison
- Analytical Sensitivity
- Analytical Specificity

N. Conclusions

Comparative testing of the ADVIA Centaur HAVT assay with the addition of the neonate and pediatric populations is substantially equivalent in principle and performance to the Predicate Device VITROS Immunodiagnostic Products Anti-HAV Total Reagent Pack cleared under 510(k) k060678.