

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

K142758

B. Purpose for Submission:

To expand the Intended Use Statement to include pediatric and neonatal patients.

C. Measurand:

Total antibodies to Hepatitis A Virus (HAV).

D. Type of Test:

Qualitative, competitive immunoassay using direct chemiluminescence technology.

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

ADVIA Centaur[®] HAV Total Assay

G. Regulatory Information:

1. Regulation section:

21 CFR§866.3310; Hepatitis A virus (HAV) serological assays

2. Classification:

II

3. Product code:

LOL; Hepatitis A Test (Antibody and IgM Antibody)

4. Panel:

Microbiology

H. Intended Use:

1. Intended use(s):

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.

2. Indication(s) for use:

Same as the Intended Use.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

ADVIA Centaur[®] systems

I. Device Description:

The ADVIA Centaur HAV Total assay is a fully automated, competitive immunoassay using direct, chemiluminescent technology. The device is intended for the detection of total antibodies to HAV and uses a Fab fragment of mouse monoclonal anti-HAV labeled with biotin as capture antibody and a monoclonal antibody to HAV labeled with acridinium ester for detection. The ADVIA Centaur[®] HAV Total assay is comprised of the following reagents:

- ReadyPack[®] primary reagent pack containing ADVIA Centaur[®] HAVT Lite Reagent, Solid Phase Reagent, and Antigen Reagent
- ReadyPack ancillary reagent pack containing ADVIA Centaur HAVT Ancillary Reagent
- ADVIA Centaur HAVT Master Curve card
- ADVIA Centaur HAVT Low Calibrator
- ADVIA Centaur HAVT High Calibrator
- ADVIA Centaur systems HAVT Calibrator Assigned Value Card
- ADVIA Centaur systems HAVT quality control material
- ADVIA Centaur Ancillary Probe Wash I is a solution of sodium hydroxide
- ADVIA Centaur Wash I is phosphate buffered saline with preservatives (only in ADVIA Centaur[®] and ADVIA Centaur[®] XP)

The HAVT ReadyPacks consist of the following:

ReadyPack[®] 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 consists of 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.

ReadyPack ancillary reagent 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%)

J. Substantial Equivalence Information:

1. Predicate device name(s):

VITROS Immunodiagnostic Products Anti-HAV Total Reagent Pack

2. Predicate 510(k) number(s):

K060678

3. Comparison with predicate:

Similarities		
Item	New Device	Predicate Device
	ADVIA Centaur HAVT Assay (K142758)	VITROS Anti-HAV Total Reagent (K060678)
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	New Device	Predicate Device
	ADVIA Centaur HAVT Assay (K142758)	VITROS Anti-HAV Total Reagent (K060678)
Standardization / Traceability	Assay cutoff (Index Value 1.00) is equivalent to 20 mIU/mL standardized to the WHO 2 nd 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. The relative light units (RLUs) detected by the ADVIA Centaur System are used to calculate the Index Value from the Master Curve.

Interpretation of results

- Samples with a calculated value of less than 1.00 Index Value are considered nonreactive for antibodies to hepatitis A virus.
- Samples with a calculated value greater than or equal to 1.00 Index Value are considered reactive for antibodies to hepatitis A virus.

Assay results above the cutoff of the assay are not indicative of antibody level.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

See P040017.

b. *Linearity/assay reportable range:*

See P040017.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

See P040017.

d. *Detection limit:*

See P040017.

e. *Analytical specificity:*

See P040017.

f. *Assay cut-off:*

See P040017.

2. Comparison studies:

a. *Method comparison with predicate device:*

Pediatric testing (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 (including 95% confidence intervals) of results for reactive and nonreactive samples between the ADVIA Centaur HAVT and the comparative assay for the pediatric population is shown in the following table:

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

Comparative anti-HAV Total Assay

	<i>Positive</i>	<i>Borderline</i>	<i>Negative</i>	<i>Totals</i>	
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.

b. Matrix comparison:

For matrix comparison, data are cross-referenced to the original Premarket Approval for the ADVIA Centaur HAVT assay on the ADVIA Centaur systems (P040017).

3. Clinical studies:

a. Clinical Sensitivity:

Not Applicable.

b. Clinical specificity:

Not applicable.

c. Other clinical supportive data (when a. and b. are not applicable):

The following studies were performed to demonstrate that the neonate and pediatric (ages 2 to 21 years) populations can be used in the ADVIA Centaur HAV Total assay:

Neonate vs Adult Comparison

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)

Pediatric vs. Adult Comparison (Analytical)

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 (ages 2-21) 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)

For additional clinical data see P040017.

4. Clinical cut-off:

Not Applicable.

5. Expected values/Reference range:

See P040017.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.