

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Hepatitis C Virus (anti-HCV) Assay
Device Trade Name: ADVIA Centaur® HCV Assay
ADVIA Centaur® HCV Quality Control
Applicant's Name and Address: Bayer HealthCare LLC,
511 Benedict Avenue
Tarrytown, NY 10591-5097
Premarket Approval Application (PMA) Number: P030056
Date(s) of Panel Recommendation: None
Date of Notice of Approval to Applicant: December 22, 2004

II. INDICATIONS FOR USE

ADVIA Centaur® HCV Assay

The ADVIA Centaur® HCV assay is an *in vitro* diagnostic immunoassay for the qualitative determination of immunoglobulin G (IgG) antibodies to hepatitis C virus (HCV) in human serum and plasma (EDTA, lithium or sodium heparinized) using the ADVIA Centaur® System. The assay may be used in conjunction with other serological and clinical information to aid in the diagnosis of individuals with symptoms of hepatitis and in individuals at risk for hepatitis C infection.

ADVIA Centaur® HCV Quality Control

For *in vitro* diagnostic use in monitoring the performance of the HCV assay on the ADVIA Centaur® Systems. The performance of the HCV quality control material has not been established with any other anti-HCV assays.

III. CONTRAINDICATIONS - None

IV. WARNINGS AND PRECAUTIONS

For *in vitro* diagnostic use only. This assay has not been FDA cleared or approved for the screening of blood or plasma donors.

Warnings and precautions for ADVIA Centaur® HCV assay and ADVIA Centaur® HCV Quality Control materials are stated in the respective product labeling.

V. DEVICE DESCRIPTION

The ADVIA Centaur[®] HCV assay is an indirect 2-wash sandwich immunoassay. The sample is incubated with Solid Phase containing recombinant and synthetic peptide HCV antigens. Antigen-antibody complexes will form if anti-HCV antibody is present in the sample. Lite Reagent containing monoclonal anti-human IgG labeled with acridinium ester is used to detect anti-HCV IgG in the sample.

Sample is first incubated with Ancillary Reagent (specimen diluent) for 5 minutes at 37°C. The Solid Phase and Ready Pack Ancillary Reagent are added next and the reaction mix incubates for 18 minutes at 37°C. During this incubation biotinylated HCV antigens in the ReadyPack ancillary reagent bind to the anti-HCV antibodies in the sample and this sample anti-HCV / biotinylated HCV antigen complex binds to the streptavidin-coated microparticles in the Solid Phase. The microparticles are then held fast by a magnet and washed multiple times to remove unbound sample. Lite reagent is added next and the reaction mix incubates for 18 minutes at 37°C. The microparticles are then held fast by a magnet and washed multiple times to remove unbound Lite Reagent. The reaction mix is next reacted with acid and base to initiate a chemiluminescent reaction of the bound acridinium ester. The chemiluminescent signal is detected and quantified as relative light units (RLUs) by the photomultiplier tube (PMT) of the ADVIA Centaur Instrument. The relative light units (RLUs) detected by the ADVIA Centaur System are used to calculate the Index Value from the Master Curve. A result of reactive or nonreactive is determined according to the Index Value established with the calibrators.

Calibration

The ADVIA Centaur[®] HCV assay utilizes a factory set Master Curve. The Master Curve values are contained on the Master Curve card provided with each kit. The master curve and calibration are lot specific. The barcode reader or keyboard is used to enter the Master Curve values on the system. The 2 calibrators in the kit are run when the lot is first used or after expiration of the calibration interval (28 days). If the calibration run is valid as determined by prearranged parameters, the values are stored and used to “normalize” test values to the Master Curve.

Assay antigen/antibody Description

The host organism for the 2 recombinant HCV-encoded antigens (c200 and NS5) is *Saccharomyces cerevisiae* (yeast). Each of the recombinant antigens is a fusion protein with human superoxide dismutase (SOD). Superoxide dismutase is derived from the expression vector used in production of the recombinant antigens. The SOD portion of the recombinant antigens is 154 amino acids.

The c200 recombinant antigen is encoded by the NS3 and NS4 regions of the HCV genome. The c200 recombinant antigen contains the c33c and the c100-3 protein sequences. The c33c sequence is encoded from the NS3 region of the HCV genome and following infection with HCV, host-generated antibodies are frequently reactive with the c33c protein. Nucleotide sequence comparisons with similar viruses suggest that the NS3 region codes for the viral helicase involved in virus replication. The c100-3 sequence is encoded from the NS4 region of the HCV genome, and following infection with HCV, host-generated antibodies are frequently reactive with the c100-3 protein. The NS4 region may have a membrane binding function. The HCV-specific amino acid sequence of the c200 recombinant antigen includes residue 1192 to residue 1931. The apparent molecular weight of the c200 recombinant antigen is 97.4 kD by SDS-PAGE.

The NS5 recombinant antigen is encoded by the NS5 region of the HCV genome. Nucleotide sequence comparisons with similar viruses suggest that the NS5 region codes for the viral RNA-dependent RNA polymerase involved in virus replication. A significant number of individuals infected with HCV develop an immunologic response to NS5. The HCV-specific amino acid sequence of the NS5 recombinant antigen includes residue 2054 to residue 2995. The apparent molecular weight of the NS5 recombinant antigen is 150 kD by sodium dodecyl sulfate polyacrylamide gel electrophoresis.

The 39 amino acid synthetic peptide c22 is derived from the core region of the HCV genome. This region of the HCV genome encodes the RNA-binding nucleocapsid protein, and it is believed that this protein is involved in the formation of the viral core structure. Following infection with HCV, host-generated antibodies are frequently reactive with the c22-3 protein. The HCV-specific amino acid sequence of the c22 synthetic antigen includes residues 6 to 44. The c22 synthetic antigen is biotinylated at the N-terminus following synthesis. The molecular weight of the biotinylated c22 synthetic peptide is 4446.14 daltons as confirmed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) analysis. The sequence is also confirmed by amino acid sequencing.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Determination of the presence of anti-HCV in patients may be achieved by using a variety of commercially available, FDA licensed serological tests. Additionally, when these test results are used in combination with a physician's assessment and other laboratory test results, a diagnosis of infection with HCV can be established.

VII. MARKETING HISTORY

The ADVIA Centaur[®] HCV Assay is currently being marketed internationally in accordance with section 802 of the FD&C Act.

This product has not been withdrawn from any country for any reason: Canada, Columbia, Sweden, Norway, Finland, France, Germany, Italy, Spain, Portugal, United Kingdom, Belgium, Austria, Greece, Switzerland, south Africa, china, Hong Kong, Singapore, Malaysia, Korea, Australia and New Zealand.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The ADVIA Centaur[®] HCV ReadyPack Reagents and ADVIA Centaur[®] HCV Quality Control materials are for in vitro diagnostic use, thus there is no direct adverse effect on the patient. Failure of the product to perform as intended, or errors in the use of the product, may lead to a false result.

A false reactive (false positive) result using an anti-HCV assay is not considered a patient or public health concern because a reactive enzyme immunoassay (EIA) result in a clinical lab should be followed up with supplemental tests (e.g., strip immunoblot assay (SIA) and/or polymerase chain reaction (PCR) for detection of HCV RNA) to determine inactive or resolved infection versus active HCV replication.¹ Treatment of the patient with chronic HCV infection is initiated

¹ CDC, Recommendations for Prevention and Control of Hepatitis-C Virus (HCV) Infection and HCV-Related Chronic Disease. MMWR 1998;47 (RR-19):1-39.

only after extensive clinical, laboratory and behavioral assessment of the patient (e.g., elevated ALT levels for six months, detectable serum HCV RNA, liver biopsy with portal fibrosis, patient compliance, and abstinence from drugs and alcohol).

A false nonreactive (false negative) anti-HCV result in a diagnostic setting may lead to a patient with HCV going unidentified. Under these circumstances, there is a safety concern for both the patient and the public, since such individuals may be capable of transmitting HCV infection. However, if a patient is known to be at high risk of HCV infection, or is symptomatic, and the physician's suspicion of HCV infection is high, HCV RNA testing is often employed and is of diagnostic value, even after an initial negative anti-HCV test result.

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

Volunteer Donor Population

A population study of volunteer (presumed negative) serum and plasma specimens were used to examine the negative distribution and specificity of the ADVIA Centaur[®] HCV assay. A total of 1125 fresh and frozen samples were tested. Five samples were repeatedly reactive and 3 samples were confirmed as positive by supplemental testing (Chiron[®] RIBA[®] HCV SIA). Calculated specificity for this population was 1120/1122 (99.82%).

Sample Type	Number tested	Initial reactive	Repeat reactive	Confirmed
Serum	382	5	5	3
EDTA Plasma	120	0	0	0
Frozen serum	161	0	0	0
Frozen Plasma	462	0	0	0
Total	1125	5	5	3
	Mean	0.03		
	Standard Deviation (SD)	0.08		
	SD to Cutoff	12.10		

HCV Seroconversion Panels

A total of 23 HCV seroconversion panels were tested in the Bayer Healthcare Tarrytown facility and compared to published data. The ADVIA Centaur[®] HCV assay was at least as sensitive in the detection of seroconversion for HCV as commercially available assays.

HCV Genotype Samples

The ability of the ADVIA Centaur[®] HCV assay to detect antibodies to various HCV genotypes was assessed by testing 100 individual genotype samples. These genotype samples included 20 type 1, 20 type 2, 20 type 3, 20 type 4, 10 type 4 non-A, and 10 type 5 samples. All of the confirmed HCV positive samples were found to be reactive in the ADVIA Centaur[®] HCV assay. Additional genotype sample data generated during US Clinical Trials is presented in the "Summary of Clinical Studies" section of this PMA.

Potential Cross Reactive Specimens

A study was performed to evaluate the ADVIA Centaur[®] HCV assay for potential cross-reactivity to other disease states, viruses, microorganisms, or historically problematic specimens. A total of

204 serum and plasma specimens from 22 groups of potential cross-reactants were assayed. The vendor used FDA-approved methods to confirm the disease state of each specimen. All samples that were reactive in the ADVIA Centaur[®] HCV assay were also reactive in the Ortho 3.0 HCV assay. No significant cross-reactions were observed between the ADVIA Centaur[®] HCV assay and markers of other disease states.

Clinical Category	Number Tested	Number of Reactive Anti-HCV Results	
		ADVIA Centaur Assay	Reference Assay
Hepatitis A Infection (HAV)	5	0	0
Non-viral Liver Disease	10	1	1
Epstein-Barr Virus (EBV) IgG	10	0	0
Epstein-Barr Virus (EBV) IgM	10	0	0
Herpes Simplex Virus (HSV) IgG	10	0	0
Herpes Simplex Virus (HSV) IgM	10	0	0
Syphilis IgG	14	0	0
Human Immunodeficiency Virus (HIV1/2)	10	1	1
Varicella Zoster (VZV) IgG	10	0	0
Cytomegalovirus (CMV) IgG	10	0	0
Cytomegalovirus (CMV) IgM	3	0	0
Rubella IgG	10	0	0
Toxoplasma IgG	10	0	0
Multiparity	10	0	0
Flu Vaccine Recipient	10	2	2
Rheumatoid Arthritis (RF)	9	1	1
Anti-Nuclear Antibody (ANA) and Systemic Lupus Erythematosus (SLE)	7	0	0
Total Samples Tested	158	5	5

Endogenous Interferents

The ADVIA Centaur[®] HCV assay was tested following the guidelines described by National Committee for Clinical Laboratory Standards (NCCLS) EP7-P for interference due to high levels of endogenous substances. The effects of conjugated bilirubin at 60 mg/dL, unconjugated bilirubin at 40 mg/dL, hemoglobin at 500 mg/dL, triglycerides at 1000 mg/dL, and human serum albumin at 12 g/dL (ie, high total protein), were evaluated in serum and plasma samples. No interference was observed in the performance of the ADVIA Centaur[®] anti-HCV assay in these tests.

Precision Studies

A single-instrument NCCLS precision study was run according the NCCLS EP5-A protocol using the ADVIA Centaur[®] HCV assay. The study was set up as an evaluation of HCV assay precision versus imprecision goals and as a study of the effect of sample matrix (serum versus 5 plasma anticoagulants) on specimen precision. Frozen (-20°C) single-donor units were obtained using each of the following anti-coagulants: serum, potassium EDTA, lithium heparin, and sodium heparin.

Each unit was used to prepare a five-member panel targeting the Anti-HCV Index listed in the table below. A high titer Anti-HCV positive plasma pool was used to prepare the spiked positive panel members.

Anti-HCV Positive Plasma Pool

	INDEX	Sample
Level 1	0.0	negative, unspiked
Level 2	1.0	elevated negative/equivocal, spiked
Level 3	3.0	low positive #1, spiked
Level 4	5.0	low positive #2, spiked
Level 5	8.0	high positive, spiked

ADVIA Centaur[®] HCV assay Ready-Packs were taken from 4°C storage and placed on the Centaur[®] as needed. Each sample was run twice a day in triplicate for 20 days. A new set of sample aliquots was thawed and mixed/centrifuged for each day of the study. The results of this study are summarized below.

ADVIA Centaur[®] HCV Precision

Index Ranges	Within Run Precision (% CV)	Total Precision (%CV)
1.0 to 3.0	< 5 %	< 10 %
5.0 to 10.0	< 5 %	< 10 %

Effects of Type of Collection Tube on Matrix Data

The effects of type of collection tube and different anticoagulants on assay performance were evaluated by testing donor samples collected in different collection tubes containing anticoagulants (potassium EDTA in plastic, lithium heparin in glass and plastic, sodium heparin in glass and plastic, serum separator tubes [SST], in glass and plastic, and redtop serum tubes in glass and plastic). First, HCV negative donor samples were screened as unadulterated samples. To obtain HCV positive samples, the HCV negative donor samples were spiked with a HCV positive pool at three levels. Percent recovery was calculated by comparison to samples collected in redtop serum tubes. In this study there was no change in clinical interpretation when samples were tested using different collection tubes when compared to samples collected in redtop serum tubes. In conclusion, these collection tubes are acceptable for use with the ADVIA Centaur[®] HCV assay.

Sample Handling Studies

The sample handling studies were a series of experiments in which specimens collected in the sample matrices claimed as suitable for use in the ADVIA Centaur[®] HCV method were subjected to potential stresses and then tested using the ADVIA Centaur[®] HCV assay. Samples were subjected to potential stresses including freeze/thaw and elevated temperature storage and tested in comparison to a non-stressed control sample to determine the impact of the stress on assay accuracy. The sample handling studies described here evaluated the effect of the following patient sample-handling conditions on ADVIA Centaur[®] HCV Index Values:

1. Extended time onboard the Centaur[®] Instrument
2. Extended time in refrigerated (2 -8°C) storage
3. Extended time at room temperature (25°C) storage
4. Extended time in freezer (-20°C) storage
5. Multiple freeze thaw (-20°C/2- 8°C) cycles

Samples were collected during in-house blood draws from healthy donors in serum and plasma collection tubes with a variety of anti-coagulants. Samples were aliquoted and placed in appropriate storage/stress conditions on the day of collection. A baseline Index value for each sample was established by testing with the ADVIA Centaur[®] HCV assay on the day of collection. All percentage recoveries were calculated against the baseline (day 0) value. Results from the sample-handling studies support the claims that samples can be subjected to the following conditions and still generate accurate results when tested in the ADVIA Centaur[®] HCV assay:

1. Samples can be kept onboard the Centaur[®] instrument for at least 8 hours.
2. Samples can be stored at room temperature for at least 2 days.
3. Samples can be stored refrigerated (2-8°C) for at least 7 days.
4. Samples can be stored frozen (-20°C) for long term storage.
5. Samples can be frozen and thawed at least 4 times.

On-The-Clot Specimen Storage

A study was done to determine if storing the processed serum or plasma sample in the original collection tube ("On the Clot") rather than transferring the sample to secondary container affected the ADVIA Centaur[®] HCV Index Value. Fresh samples were drawn from 10 healthy in-house donors into serum and plasma collection tube types. The specimens were centrifuged within the recommended time and an aliquot from each primary tube was placed in another container (HCV positive specimens were carefully spiked with high positive HCV plasma before removing the aliquot). The primary (collection) tubes and the removed aliquots were then stored at 2-8°C and tested side by side in the ADVIA Centaur[®] HCV assay on Days 0, 1, 3, 6 and 8 after collection. There was no evidence of any effect of storage of the sample in the primary serum and EDTA collection tubes for up to 7 days at 2-8°C.

Stability Studies

Real-time stability studies were carried out for Centaur[®] ReadyPack reagents, calibrators, and controls. Three lots of ADVIA Centaur[®] HCV assay reagents, calibrators and controls were placed on real time stability studies. All kits and reagents were stored at the recommended storage temperature of 2 to 8°C. Reagents and calibrators are evaluated at several checkpoints post manufacturing date.

The real time stability studies support a claim of 12 months of stability at 2-8°C for the ADVIA Centaur[®] HCV reagents/calibrators and the ADVIA Centaur[®] HCV Quality Control materials.

Calibrator and Control Shipping Stability Studies

A calibrator and control shipping study has also been performed on two lots. The ADVIA Centaur[®] HCV assay calibrators and controls underwent three freeze/thaw cycles with no adverse effects.

Microbiology Studies

The ADVIA Centaur® HCV reagents contain amphotericin, gentamicin, and Na Azide as preservatives to protect against adventitious contamination by microorganisms. The ADVIA Centaur® HCV calibrators and controls contain ProClin and Na Azide as a preservative to protect against adventitious contamination by microorganisms. Reagents and Controls were challenged in a study conducted according to USP 23/NF 18. The preservative study results indicated complete and effective elimination of some of the microorganisms

A performance microbial challenge was performed using one lot of ADVIA Centaur® HCV assay reagents, calibrators, and controls. Reagents and controls were inoculated with two pools of microbes then run on the Centaur® instrument at time 0 (Baseline), 30 days and 60 days. The inoculated reagents and controls give results consistent with baseline (not inoculated) at day zero, day 30 and day 60. Controls and MDPs recover within their release ranges.

Reagent Compatibility Testing

The purpose of this study was to confirm there are no primary reagent interactions for assays that share the same reagent probe, and might therefore have been susceptible to reagent carryover affects. Mitigation of any interference identified was accomplished through Test definition (Tdef) scheduling options, using multiple water washes, or, in rare occasions, a Wash Pack with a solution other than water may have been required.

The ADVIA Centaur® HCV assay was evaluated for its potential affect on all other assays using the same reagent probes and for the affect of all the other assay reagents on the ADVIA Centaur® HCV assay. To be accepted there must be <5% difference in Index between test and control, or no statistically significant change in Index.

There were no compatibility issues between this assay and any of the assays sharing the same reagent probe.

X. SUMMARY OF CLINICAL STUDIES

The prospective study population for the ADVIA Centaur® HCV assay consisted of 2181 patients. Of these 2181 patients, 1335 patients (61.21%) were from patients considered at risk for hepatitis (the high risk population) due to lifestyle, behavior, occupation, disease state (eg, infection with human immunodeficiency virus [HIV], transplant recipient, dialysis patient, and hemophilia), or due to known exposure events. A total of 846 patients (38.79%) were from individuals exhibiting signs and/or symptoms of hepatitis infection (the signs and symptoms population). The prospective study population was 44.66% Caucasian, 25.81% Hispanic, 22.24% African American, 3.12% Asian, and 4.17% from unknown or other ethnicity. The majority of patients were male (55.62% male and 44.38% female). The mean age was 45.4 years (range of 12 to 82 years). Patients in the prospective study population were from the following geographic regions: Florida (37.09%), Texas (32.10%), New York (19.58%), California (7.79%), and 3.44% were from an unknown or other geographic region.

The HCV status for each patient was determined from results of a reference assay for the detection of anti-HCV and the Chiron® RIBA® HCV SIA. To determine infection with hepatitis B virus (HBV), the following tests were performed for 6 HBV markers: hepatitis B virus surface antigen (HBsAg), hepatitis B virus e antigen (HBeAg), total antibody to hepatitis B virus core antigen (Anti-HBc Total), IgM antibody to hepatitis B virus core antigen (anti-HBc IgM), total antibody to HBeAg (Anti-HBe), and total antibody to hepatitis B virus surface antigen (anti-HBs) (quantitative). Based on the results of HBV marker testing, the HBV infection was determined to be acute, chronic, in early recovery, or in recovery. Infection with hepatitis A virus (HAV) was determined from the medical history of the patient. Reference assays were performed using 15
USFDA-approved methods.

Testing for anti-HCV using the reference method and the ADVIA Centaur® HCV assay were performed at each of 3 testing sites (Florida, Texas, and New York). Patients were enrolled at the 3 testing sites and 1 additional clinical site.

A total of 1335 of 2181 patients (61.21%) in the prospective population were asymptomatic for HCV infection at enrollment. The asymptomatic population included patients at high risk of HCV infection due to lifestyle, behavior, occupation, disease state (eg, infection with HIV, transplant recipient, dialysis patient, and hemophilia), or due to known exposure events. In the asymptomatic population, 469 of 1335 patients (35.13%) were tested at the Florida site, 445 of 1335 patients (33.33%) were tested at the Texas site, and 421 of 1335 patients (31.54%) were tested at the New York site. The asymptomatic study population was 40.30% Caucasian, 26.30% Hispanic, 26.14% African American, 2.92% Asian, and 4.34% from unknown or other ethnicity. The majority of patients in the asymptomatic population were male (52.88% male and 47.12% female). The mean age in the asymptomatic population was 41.8 years (range of 12 to 82 years).

A total of 435 of 1335 patients (32.58%) in the asymptomatic population were reactive in the ADVIA Centaur® HCV assay. (Samples were considered reactive if they were reactive in the ADVIA Centaur® HCV assay upon repeat testing). For the asymptomatic population, the following percentages of patients at each testing site had reactive ADVIA Centaur® HCV results: 32.41% at Florida, 23.15% at Texas, and 42.76% at New York.

The ADVIA Centaur® HCV assay results for the asymptomatic population for all sites combined by age group and gender are summarized in the following table.

A total of 660 of 846 patients (78.01%) in the signs and symptoms population were repeatedly reactive in the ADVIA Centaur® HCV assay. For the signs and symptoms population, the following percentages of patients at each testing site had repeatedly reactive ADVIA Centaur® HCV results: 78.41% at Florida, 75.71% at Texas, and 79.80% at New York.

Prospective Study Results

The HCV infection status of patients in the prospective population was found to be not infected, infected, or not determined by testing with the reference anti-HCV assay and the confirmatory Chiron RIBA HCV 3.0 SIA assay. The algorithm for assignment of HCV status is presented in the following table:

Reference anti-HCV assay result	CHIRON RIBA HCV 3.0 SIA Result	HCV Status
Repeatedly Reactive (RR)	Positive (P)	INFECTED
Repeatedly Reactive (RR)	Indeterminate (I)	NOT DETERMINED
Repeatedly Reactive (RR)	Negative (N)	NOT INFECTED
Nonreactive (N)	Not applicable (NA)	NOT INFECTED

The results of ADVIA Centaur[®] HCV testing and reference HCV testing are shown in the following table by presumptive diagnosis and risk of HCV infection for patients in the prospective population who were found to be infected, not determined, and not infected by the algorithm described in the previous table. The categories of risk of HCV infection were ordered according to clinical evaluation and are listed in the table from highest risk to lowest risk of HCV infection. Each subject was assigned only one risk factor (the highest).

Bayer ADVIA Centaur® HCV										
HCV Status and ADVIA Centaur® HCV Assay Results for the Prospective Population by Presumptive Diagnosis and Risk Groups for Hepatitis										
ADVIA Centaur® HCV Assay vs. HCV Status										
All Testing Sites										
Presumptive Diagnosis and Risk Groups	HCV Status ^a									Total ^c
	Infected			Not Determined			Not Infected			
	ADVIA Centaur® HCV Assay ^b			ADVIA Centaur® HCV Assay			ADVIA Centaur® HCV Assay			
	Reacti ve	Equivoc al	Nonrea ctive	Reacti ve	Equivoc al	Nonrea ctive	Reacti ve	Equivoc al	Nonreactiv e	
	N	N	N	N	N	N	N	N	N	
Signs and Symptoms	632	0	0	23	0	1	5	0	185	846
Hemophiliac	77	0	0	1	0	0	0	0	3	81
Intravenous drug user, current or past	192	0	0	4	0	0	3	0	55	254
Dialysis	30	0	0	5	0	0	2	0	163	200
Transfusion/Trans-plant	66	0	0	1	0	0	0	2	172	241
High Risk Sex ^d	21	0	0	4	0	0	1	1	197	224
Healthcare Worker	8	0	0	0	0	0	0	0	201	209
HIV infected	1	0	0	0	0	0	0	0	10	11
Other ^e	17	0	0	1	0	0	1	1	95	115
None Specified	0	0	0	0	0	0	0	0	0	0
Overall	1044	0	0	39	0	1	12 ^f	4 ^g	1081	2181

- a Final HCV status was based on the reference test results and Chiron® RIBA® supplemental testing of samples that were repeatedly reactive by reference anti-HCV assay testing.
- b Final ADVIA Centaur® HCV status was based on the initial test result and retest of initially reactive samples.
- c Total number of test results by risk population.
- d The high risk sex group includes patients with a diagnosis of a sexually transmitted disease, a sexual partner with a history of hepatitis, same sex sexual preference, multiple sex partners, HIV infected partner, or prostitutes.
- e The Other risk group includes patients with the following risk factors: sharing straw cocaine, tattoo, history of incarceration, body piercing, family history of hepatitis, immunocompromised patient, tattoo artist, mortician, or other known hepatitis exposure event.
- f These 12 patients had nonreactive results in the reference anti-HCV assay and/or had nonreactive results in the Chiron® RIBA® HCV 3.0 SIA assay and were considered to be HCV not infected. Eleven of these 12 patients had reactive results in the ADVIA Centaur® HCV assay, 4 patients had reactive results in both the ADVIA Centaur® HCV and the reference anti-HCV assays, and 1 patient had nonreactive results in the ADVIA Centaur® anti-HCV assay. (Although this patient was initially nonreactive in the ADVIA Centaur® HCV assay, retest Index Values were reactive [> 1.0] and the patient was considered to have reactive results in the Centaur® method).
- g These 4 patients had nonreactive results in the reference anti-HCV assay and/or had nonreactive results in the Chiron® RIBA® HCV 3.0 SIA assay and were considered to be HCV not infected. All of these 4 patients had equivocal results in the ADVIA Centaur® HCV assay.

Note The data described in footnotes *f* and *g* did not result in any modifications to the calculations of percent agreement described below.

The HCV status of 40 patients in the prospective population was considered to be not determined. Samples from these patients were repeatedly reactive in the reference anti-HCV assay and were indeterminate in the Chiron RIBA® HCV 3.0 SIA assay. Additional testing for these patient samples was performed by using the COBAS AMPLICOR® HCV test, version 2.0 (COBAS AMPLICOR HCV-NAT). Results of the ADVIA Centaur® anti-HCV testing, COBAS AMPLICOR HCV-NAT supplemental testing, and HCV status as determined by HCV-NAT testing are shown in the following table.

The percent agreements between the ADVIA Centaur® HCV assay results, including the upper and lower 95% confidence intervals, and HCV status as determined by reference anti-HCV assay testing for patients in the prospective population were determined. The positive, negative, and overall percent agreements were calculated as follows:

Positive percent agreement =

$$\frac{\text{Number of reactive ADVIA Centaur® HCV results in agreement with infected HCV status}}{\text{Total number of patients with infected HCV status}} \times 100$$

Negative percent agreement =

$$\frac{\text{Number of nonreactive ADVIA Centaur® HCV results in agreement with not infected HCV status}}{\text{Total number of patients with not infected HCV status}} \times 100$$

Overall percent agreement =

$$\frac{\text{Number of ADVIA Centaur® HCV results in agreement with HCV status}}{\text{Total number of infected HCV status and not infected HCV status}} \times 100$$

The percent positive and percent negative agreements between the ADVIA Centaur® anti-HCV assay results and HCV status in the prospective population are presented by presumptive diagnosis and risk of 19

HCV infection in the following table. For calculations of percent positive and percent negative agreements, patient samples that were reactive in the ADVIA Centaur® HCV assay and were found to have not determined HCV status after Chiron® RIBA® HCV 3.0 SIA testing and COBAS AMPLICOR® HCV-NAT testing were considered to have not infected HCV status (12 samples). Samples that were nonreactive in ADVIA Centaur® HCV assay and found to have not determined HCV status after Chiron® RIBA® HCV 3.0 SIA testing and COBAS AMPLICOR® HCV-NAT testing were considered to have infected HCV status (1 sample).

The overall positive percent agreement between the ADVIA Centaur® HCV assay results and HCV infected status for the prospective population was 99.91% (1071 of 1072 patients). The overall negative percent agreement between the ADVIA Centaur® HCV assay results and HCV not infected status for the prospective population was 97.48% (1081 of 1109 patients). There were no differences among the presumptive diagnosis and risk groups for HCV infection in the percent positive or percent negative agreements.

Samples from patients in the prospective population who were determined to be HBV infected or HAV infected were tested in the ADVIA Centaur® HCV assay and reference anti-HCV assay. Hepatitis B infection was determined to be acute, chronic, early recovery, recovery, or recovered stages of infection by HBsAg, HBeAg, anti-HBc Total, anti-HBc IgM, anti-HBeAg, and anti-HBs Total assays. Hepatitis A infection was determined from the medical history of the patient. Results of the anti-HCV assays were presented for patients with HCV infected status, HCV not determined status, and HCV not infected status by presumptive diagnosis and risk groups for HCV infection in the following table.

Bayer ADVIA Centaur® HCV										
HCV Status and ADVIA Centaur® HCV Assay Results Among HBV Infected Patients as Determined by Marker Testing^a										
ADVIA Centaur® HCV Assay vs. HCV Status										
All Testing Sites										
Presumptive Diagnosis and Risk Groups	HCV Status^b									Total^d
	Infected			Not Determined			Not Infected			
	ADVIA Centaur® HCV Assay^c			ADVIA Centaur® HCV Assay			ADVIA Centaur® HCV Assay			
	Reactive	Equivocal	Nonreactive	reactive	Equivocal	Nonreactive	Reactive	Equivocal	Nonreactive	
	N	N	N	N	N	N	N	N	N	
Signs and Symptoms	161	0	0	3	0	0	1	0	99	264
Hemophiliac	1	0	0	0	0	0	0	0	0	1
Intravenous drug user, current or past	65	0	0	0	0	0	1	0	2	68
Dialysis	5	0	0	1	0	0	0	0	20	26
Transfusion/Trans-plant	6	0	0	0	0	0	0	2	19	27
High Risk Sex ^e	7	0	0	3	0	0	0	0	35	45
Healthcare Worker	1	0	0	0	0	0	0	0	10	11
HIV infected	0	0	0	0	0	0	0	0	4	4
Other ^f	1	0	0	0	0	0	0	0	19	20
None Specified	0	0	0	0	0	0	0	0	0	0
Overall	247	0	0	7	0	0	2	2	208	466

-
- a Hepatitis B infected patients included acute, chronic, early recovery, recovery, and recovered stages of infection.
 - b Final HCV status was based on the reference test results and Chiron® RIBA® supplemental testing of samples that were repeatedly reactive by reference anti-HCV assay testing.
 - c Final ADVIA Centaur® HCV status was based on the initial test result and retest of initially reactive samples.
 - d Total number of test results by risk population.
 - e The high risk sex group includes patients with a diagnosis of a sexually transmitted disease, a sexual partner with a history of hepatitis, same sex sexual preference, multiple sex partners, HIV infected partner, or prostitutes.
 - f The Other risk group includes patients with the following risk factors: sharing straw cocaine, tattoo, history of incarceration, body piercing, family history of hepatitis, immunocompromised patient, tattoo artist, mortician or other known hepatitis exposure event.

Among patients in the prospective population who had ongoing or previous HBV infection (466 patients), the overall positive percent agreement between the ADVIA Centaur® HCV method and HCV infected status was 100.00% (247 of 247 HCV infected patients). The overall negative percent agreement between the ADVIA Centaur® HCV assay and HCV not infected status was 98.11% (208 of 212 HCV not infected patients) among patients in the prospective population who had ongoing or previous HBV infection.

Bayer ADVIA Centaur® HCV										
HCV Status and ADVIA Centaur® HCV Assay Results Among HAV Infected Patients ^a										
ADVIA Centaur® HCV Assay vs. HCV Status										
All Testing Sites										
Presumptive Diagnosis and Risk Groups	HCV Status ^b									Total ^d
	Infected			Not Determined			Not Infected			
	ADVIA Centaur® HCV Assay ^c			ADVIA Centaur® HCV Assay			ADVIA Centaur® HCV Assay			
	Reactive	Equivocal	Nonreactive	Reactive	Equivocal	Nonreactive	reactive	Equivocal	Nonreactive	
	N	N	N	N	N	N	N	N	N	
Signs and Symptoms	26	0	0	1	0	0	0	0	19	46
Hemophiliac	0	0	0	0	0	0	0	0	0	0
Intravenous drug user, current or past	2	0	0	0	0	0	0	0	2	4
Dialysis	0	0	0	0	0	0	0	0	2	2
Transfusion/Trans-plant	0	0	0	0	0	0	0	0	4	4
High Risk Sex ^e	2	0	0	0	0	0	0	0	7	9
Healthcare Worker	0	0	0	0	0	0	0	0	9	9
HIV infected	0	0	0	0	0	0	0	0	0	0
Other ^f	0	0	0	0	0	0	0	0	0	0
None Specified	0	0	0	0	0	0	0	0	0	0
Overall	30	0	0	1	0	0	0	0	43	74

a Patients with hepatitis type A.

b Final HCV status was based on the reference test results and Chiron® RIBA® supplemental testing of samples that were repeatedly reactive by reference anti-HCV assay testing.

c Final ADVIA Centaur® HCV status was based on the initial test result and retest of initially reactive samples.

d Total number of test results by risk population.

e The high risk sex group includes patients with a diagnosis of a sexually transmitted disease, a sexual partner with a history of hepatitis, same sex sexual preference, multiple sex partners, HIV infected partner, or prostitutes.

f The Other risk group includes patients with the following risk factors: sharing straw cocaine, tattoo, history of incarceration, body piercing, family history of hepatitis, immunocompromised patient, tattoo artist, mortician or other known hepatitis exposure event.

Among patients in the prospective population who had ongoing or previous HAV infection (74 patients), the overall positive percent agreement between the ADVIA Centaur® HCV method and HCV infected status was 100.00% (30 of 30 HCV infected patients), and the overall negative percent agreement with HCV not infected status was 100.00% (43 of 43 HCV not infected patients).

Seroconversion Study

Twenty commercially available seroconversion panels were tested with the ADVIA Centaur® HCV assay and the reference anti-HCV assay.

A summary of seroconversion results is presented in the following table.

Bayer ADVIA Centaur® HCV Days to Evidence of HCV Infection Seroconversion Panels

Panel ID	Reference anti-HCV assay ^a		Centaur® anti-HCV Assay ^b			Difference in Days to Anti-HCV Reactive Results ^c Reference – Centaur®
	N ^d	R ^e	N ^d	E ^f	R ^e	
SC0400	11	14	11		14	0
SC0406	0	9	0		9	0
PHV905	11	14	7		11	3
6211	171	182	171		182	0
6213	37	43	35		37	6
6215	10	20	10		20	0
6222	36	40	36		40	0
6216	17	23	17		23	0
6226	37	39	32		37	2
6229	10	17	10		17	0
9058	7	10	7		10	0
6228	24	28	28		31	-3
9041	31	62	31		62	0
6227	46	74	46		74	0
9054	77	82	77		82	0
9047	21	28	21		28	0
SC0403	0	6	0		6	0
PHV908	13	19	5	11	13	6

**Bayer ADVIA Centaur® HCV
Days to Evidence of HCV Infection
Seroconversion Panels**

6212	12	14	0		12	2
6214	25	30	25		30	0

- a ORTHO HCV V3.0 interpreted results: Reactive (R), or Nonreactive (N)
- b ADVIA Centaur® interpreted results: Reactive (R), Equivocal (E), or Nonreactive (N)
- c The dates of the first reactive test results were compared in the reference assay and ADVIA Centaur® assay: if the first reactive test result occurred on the same day then difference = 0, if Centaur® had an earlier date then the difference was positive, otherwise negative.
- d Post bleed day of last nonreactive result, usually denoted previous bleed from first reactive result.
- e Post bleed day of first reactive result.
- f Post bleed day of first equivocal result.

Note: Bleed day is calculated as the blood draw date for the appropriate result minus the date of first blood draw for the panel. The first draw date was bleed day 0.

Compared to the reference assay results, the first reactive time point for the ADVIA Centaur® HCV assay occurred earlier in 5 panels, at the same time in 14 panels, and later in 1 panel.

Overall, compared to the reference anti-HCV assay, the ADVIA Centaur® HCV assay demonstrated efficacy for the detection of the appearance of anti-HCV following HCV infection.

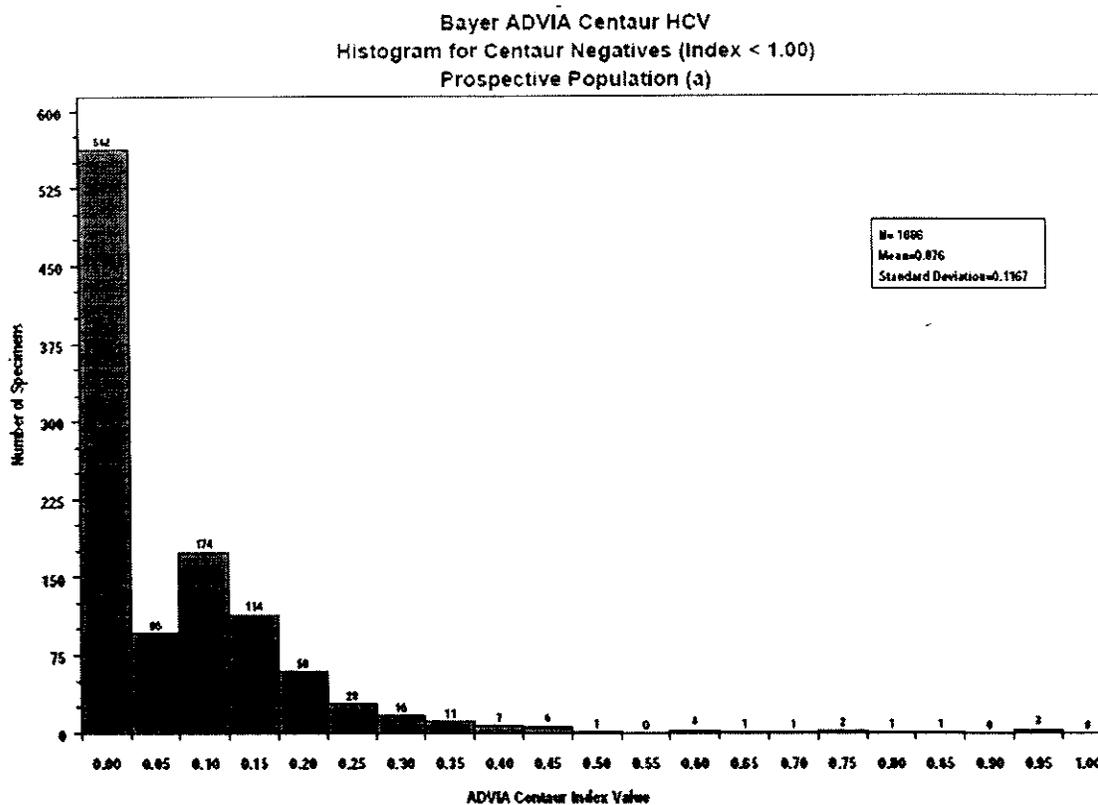
A panel of 25 commercially available samples from individuals with known HCV genotypes was tested in the ADVIA Centaur® HCV and reference anti-HCV assays. The certificate of analysis for the genotype panel presented data for HCV genotype (TrueGene® NS5B and INNO-LIPA® HCV II tests), HCV viral load (CA HCM Monitor® and Quantiplex® HCV 2.0 tests), and HCV antibody levels (HCV 2.0 E1A® and RIBA® tests). All samples tested positive for the presence of HCV.

Several HCV genotypes were detected in samples from 25 individuals using 2 genotyping assays. The following HCV genotypes were identified by both genotyping assays: 1a in 6 individuals; 1b in 4 individuals; 2b in 5 individuals; 3a in 2 individuals; 5a in 1 individual, and 6a in 1 individual. In addition to the detection of the 3a genotype by both methods for 2 individuals, the 3a genotype was also detected by 1 method (INNO-LIPA® HCV II) only for 2 individuals. The 2 genotyping tests yielded different genotype results for 4 samples: 1a versus 1b; 4a versus 4; 4a versus 4c/4d; and 4a versus 4h.

All 25 samples in the genotype panel were reactive in the ADVIA Centaur® HCV and reference anti-HCV assays.

Distribution of Negative Index Values Relative to the Cut-off Index Value

The Index Values for patients in the prospective population who had negative results in the ADVIA Centaur® HCV assay are shown in the following figure. Data are shown relative to a positive Index Value (> 1.0) and an equivocal Index value (≥ 0.8 to < 1.0).



- a Prospective population includes subjects with hepatitis by presumptive diagnosis and subjects with risk factors for hepatitis infection.

The mean \pm SD for negative Index Values in the prospective population was 0.076 ± 0.1167 . The mean negative Index Value was 8.57 standard deviations lower than the positive cut-off value (Index Value = 1.0; values ≥ 1.0 were considered positive).

Precision and Reproducibility Study

The ADVIA Centaur® HCV precision and reproducibility study was performed at 3 external sites utilizing 2 reagent lots per site. Three reagent lots were used for the study. A 5-member panel and controls were assayed in replicates of 5 on a single run per day over 6 days for each lot. The study was completed with a single calibration of the assay (one calibration interval). Standard deviation and percent CV were calculated for within run, between run, and total.

The data from all 3 sites and from all 3 reagent lots were combined to achieve SD and percent CV for within run, between run, between testing site, between lot, and total. The precision estimates were derived from variance component analysis. The reproducibility results are presented in the following table.

Bayer ADVIA Centaur® HCV Assay											
Reproducibility											
Between Testing Sites and Between Reagent Lots Estimates											
(Across All Reagent Lots and All Testing Sites)											
Panel Member	Mean ADVIA Centaur® HCV Index Value	Within Run ^a		Between Run ^b		Between Testing Site ^c		Between Lot ^d		Total ^e	
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
1	0.03	0.004	NA	0.005	NA	0.041	NA	0.011	NA	0.043	NA
2	1.22	0.066	5.43	0.076	6.23	0.000	0.00	0.076	6.21	0.126	10.34
3	3.95	0.177	4.48	0.288	7.29	0.070	1.77	0.363	9.19	0.501	12.68
4	6.32	0.267	4.22	0.376	5.95	0.221	3.49	0.718	11.36	0.881	13.94
5	9.56	0.716	7.49	0.553	5.78	0.494	5.16	0.855	8.94	1.339	14.00
Negative Control	0.08	0.014	NA	0.012	NA	0.032	NA	0.057	NA	0.068	NA
Positive Control	5.72	0.404	7.06	0.328	5.73	0.387	6.76	0.406	7.09	0.765	13.36

a Variability of the assay performance within day (all testing sites and reagent lots).

b Variability of the assay performance between days (all testing sites and reagent lots).

c Variability of the assay performance between testing sites (from testing site to testing site).

d Variability of the assay performance between reagent lots (from reagent lot to reagent lot, across all testing sites).

e Variability of the assay performance incorporating all testing sites, all reagent lots, and all days.

NA = Not applicable

Note: 5 replicates per panel in 1 run per day for 6 days

Paired Matrix Study

Using patients from the prospective population, matched serum, EDTA, and lithium heparin specimens were collected. Serum and plasma were tested in replicates of 3 per sample type using the ADVIA Centaur® HCV assay and appropriate assay controls. Edetic acid and lithium heparin were evaluated against serum (control) to determine matrix equivalency.

Results of the Paired Matrix Study support the use of EDTA and lithium heparin as anticoagulants. Samples collected with EDTA show 0.2% bias when compared to serum, and samples collected with lithium heparin show 0.2% bias when compared to serum. Comparisons of the mean control serum Index Value to the mean lithium heparin Index Value and to the mean EDTA Index Value showed no clinically significant differences. Results of the paired matrix study are summarized in the following table.

Summary of Clinical Studies

The following pattern of result interpretation was established on the basis of information collected from the clinical studies of the ADVIA Centaur® HCV assay:

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Multicentered clinical studies were conducted in the US. The ADVIA Centaur® HCV assay performed with clinical sensitivity and specificity comparable to current commercially available licensed assays.

- In asymptomatic patients (ie, patients at high risk of HCV infection due to lifestyle, behavior, occupation, disease state [eg, infection with HIV, transplant recipient, dialysis patient, and hemophilia], or due to known exposure events), 435 of 1335 patients (32.58%) were reactive in the ADVIA Centaur® HCV assay (Samples were considered reactive if they were reactive in the ADVIA Centaur® HCV assay upon repeat testing). In symptomatic patients (ie, patients with a presumptive diagnosis of HCV infection on the basis of signs and symptoms of infection), repeatedly reactive results in the ADVIA Centaur® HCV assay were observed for 660 of 846 patients (78.01%).
- The overall positive percent agreement between the ADVIA Centaur® HCV method and infected status was 99.91% in the high risk and signs and symptoms populations (i. e, the prospective population). The overall negative percent agreement between the ADVIA Centaur® HCV assay and HCV not infected status was 97.48% in the prospective population.
- Among patients in the prospective population who had ongoing or previous HBV infection (466 patients), the overall positive percent agreement between the ADVIA Centaur® HCV method and HCV infected status was 100.00% (247 of 247 HCV infected patients). The overall negative percent agreement between the ADVIA Centaur® HCV assay and HCV not infected status was 98.11% (208 of 212 HCV not infected patients) among patients in the prospective population who had ongoing or previous HBV infection. For patients in the prospective population who had ongoing or previous HAV infection (74 patients), the overall positive percent agreement between the ADVIA Centaur® HCV method and HCV infected status was 100.00% (30 of 30 HCV infected patients), and the overall negative percent agreement with HCV not infected status was 100.00% (43 of 43 HCV not infected patients).
- The ability of the ADVIA Centaur® HCV assay to detect HCV infections was demonstrated with the seroconversion panel evaluation. When the ADVIA Centaur® HCV result was compared to the reference assay results, the first reactive time point for the ADVIA Centaur® HCV assay occurred earlier in 5 panels, at the same time in 14 panels, and later in 1 panel.

- Results of an evaluation of an HCV genotype panel showed that the ADVIA Centaur® HCV and reference anti-HCV assays detected HCV infection with several different HCV genotypes: 1a, 1b, 2b; 3a; 5a; and 6a.
- Precision and reproducibility of the ADVIA Centaur® HCV assay was good with minor variability from run to run, day to day, or reagent lot to reagent lot.
- Paired Matrix Study results support the use of human serum, EDTA plasma, and lithium heparin plasma specimens for testing in the ADVIA Centaur® HCV assay.

The results from both the non-clinical and clinical studies indicate that the ADVIA Centaur® anti-HCV assay can be used safely and effectively for the qualitative in vitro determination of antibodies to HCV in human serum and plasma. The ADVIA Centaur® HCV assay may be used to define the clinical status of patients known to be infected with HCV or with other HBV, HAV, and anti-HCV assays to form a panel for the diagnosis of patients presenting with symptoms of viral hepatitis and in individuals at risk for hepatitis C infection.

Safety and Benefit/Risk Analysis

As a diagnostic test, the ADVIA Centaur® HCV assay involves removal of blood from an individual for testing purposes. This test presents no more of a safety hazard to an individual than is presented to an individual who is having their blood drawn for any other diagnostic evaluations.

The benefits to HCV-infected individuals tested by these assays outweigh any potential adverse event or risk to the patient or user due to assay malfunction or operator error.

The potential risks encountered with in vitro diagnostic tests are not unusual in the clinical laboratory setting. Appropriate warnings for these risks are contained in the labeling and package inserts for these devices. Standard good laboratory practices are considered sufficient to mitigate the risks to the end user.

XIV. PANEL RECOMMENDATION

In accordance with the provisions of section 515 (c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Microbiology Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XV. CDRH DECISION

FDA issued an approval order on December 22, 2004.

The applicant's manufacturing facility inspected on May 11, 2004 in New York and April 28, 2004 in Massachusetts and was found to be in compliance with the Quality Systems Regulation (21 CFR 820).

XVI. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.