Summary of Safety and Effectiveness

I. General Information

Device Generic Name
Antibody to human immunodeficiency virus types 1, including Group O, and/or type 2 (ADVIA Centaur® HIV 1/O/2 Enhanced Assay)

Device Trade Name
ADVIA Centaur ® HIV 1/O/2 Enhanced Assay

Name and Address of Applicant

Bayer HealthCare LLC
511 Benedict Avenue
Tarrytown, NY 10591-5097

PMA Number BP050030

Date of Panel Recommendation
****TBD****

Date of Notice of Approval to Applicant
****TBD****

II. Indications for Use

The ADVIA Centaur HIV 1/O/2 Enhanced assay is an *in vitro* diagnostic immunoassay for the qualitative determination of antibodies to the human immunodeficiency virus type 1, including Group O, and/or type 2 in serum or plasma (potassium EDTA, lithium or sodium heparinized, ACD) using the ADVIA Centaur System.

This product is not intended for testing or screening pooled specimens from more than one individual, or for use in screening blood or plasma donor. Purchase of this product does not convey any right or license under any relevant patents to use the product for testing or screening pooled blood specimens from more than one individual or for use in screening blood or plasma donors.

III. Device Description

Summary and Explanation of the Test

The ADVIA Centaur HIV 1/O/2 Enhanced assay is an antigen bridging microparticle chemiluminometric immunoassay used for the detection of antibodies to the human immunodeficiency virus type 1, including Group O, and/or type 2 in serum or plasma.

The ADVIA Centaur HIV 1/O/2 Enhanced assay uses yeast recombinant derived antigens corresponding to the viral envelope and core proteins. Recombinant antigens include an HIV-1 envelope protein (gp41/120), an HIV-1 core protein (p24), and an HIV-2 envelope protein (gp36). A synthetic peptide is added for the detection of antibodies to HIV-1 group O.

The primary purpose of the ADVIA Centaur HIV 1/O/2 Enhanced assay is to aid in the diagnosis of HIV infection and AIDS. Specimens that are initially reactive should be retested in duplicate. Repeat reactivity is highly predictive of the presence of antibody to HIV-1 and/or HIV-2 in specimens from people at risk for HIV infection, and should be followed-up with appropriate supplemental tests for HIV-1 and HIV-2 antibody before making a diagnosis of HIV infection.

Assay Principle and Format

The ADVIA Centaur HIV 1/O/2 Enhanced assay is a two wash antigen sandwich immunoassay in which antigens are bridged by antibody present in the patient sample. The Solid Phase contains a preformed complex of streptavidin coated paramagnetic microparticles and biotinylated HIV-1 and HIV-2 recombinant antigens and Group O peptide antigen. This reagent is used to capture anti-HIV-1 and/or HIV-2 antibodies in the specimen. The Ancillary Lite Reagent and Lite Reagent contain acridinium ester labeled HIV-1 and HIV-2 recombinant antigens and Group O peptide antigen used to detect anti-HIV-1 and/or HIV-2 antibodies bound to the Solid Phase in the sample.

The system automatically performs the following steps:

- dispenses 50 µL of specimen into a cuvette and incubates for 6 minutes at 37°C
- dispenses 100 µL of Solid Phase and 50 µL of Ancillary Lite Reagent and incubates for 18 minutes at 37°C
- separates the Solid Phase from the mixture and aspirates the unbound reagent
- washes the cuvette with Wash 1
- dispenses 50 µL of Lite Reagent, incubates the mixture for 18 minutes at 37°C
- separates the Solid Phase from the mixture and aspirates unbound reagent
- washes the cuvette with Wash 1
- dispenses 300 µL each of Acid Reagent and Base Reagent to initiate the chemiluminescent reaction
- reports results in index values

A direct relationship exists between the amount of HIV 1/O/2 antibody activity present in the specimen and the amount of relative light units (RLUs) detected by the system. A result of reactive or nonreactive is determined according to the Index Value established with the calibrators. Refer to *Interpretation of Results* for a description of

the Cutoff Value calculation.

Calibration

The ADVIA Centaur HIV 1/O/2 Enhanced assay utilizes a factory set Master Curve. The Master Curve values are contained on the Master Curve card provided with each kit. For calibration of the ADVIA Centaur HIV 1/O/2 Enhanced assay, use EHIV Calibrators provided with each kit. The calibrators are matched to the ReadyPack primary reagent pack.

IV. Contraindications, Warnings, and Precautions

For in vitro diagnostic use only.

No known contradictions

Warnings and precautions for ADVIA Centaur ® HIV 1/O/2 Enhanced Assay are stated in the product labeling.

V. Alternate Practices and Procedures

Determiniation of the presence of antibodies to HIV 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 HIV can be established.

VI. Marketing History

The ADVIA Centaur HIV 1/O/2 Enhanced Assay is currently being marketed internationally in accordance with section 802 of the Food Drug and Cosmetic Act in the following countries or regions: France, Germany, Italy, Spain, Portugal, UK, Belgium, Netherlands, Austria, Greece, Switzerland, Poland, Hungary, Czech Republic, Slovakia, Middle East, Russia, Africa, South Africa, Sweden, Norway, Finland, Malaysia, Korea and New Zealand.

This product has not been withdrawn from any of these markets for any reason.

VII. Potential Adverse Effects of the Device on Health

The ADVIA Centaur HIV 1/O/2 Enhanced ReadyPack Reagents, Calibrators, and Controls 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 HIV 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)). Treatment of the individual with HIV infection is initiated after clinical, laboratory (e.g., low CD4 and/or T cell count) and behavioral assessment of the individual.

A false nonreactive (false negative) HIV result in a diagnostic setting may lead to an individual with HIV 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 HIV infection. However, if an individual is known to be at high risk of HIV

infection, or is symptomatic, and the physician's suspicion of HIV infection is high, HIV follow-up testing is recommended.

VIII. Summary of Non-Clinical Studies

Laboratory Studies

The following laboratory studies were conducted to determine the performance characteristics of the ADVIA Centaur HIV 1/O/2 Enhanced assay. These laboratory studies included potential cross reactive specimens, endogenous interferences, matrix and collection tube type effects, sample handling, stability, microbial studies and instrument studies.

Potentially Cross Reactive Sample Categories

The ADVIA Centaur HIV 1/O/2 Enhanced assay was evaluated for potential cross-reactivity with other viral infections and disease state specimens. Specimens were obtained from the following vendors: ProMedDx LLC, Norton, MA; Teragenix, Ft. Lauderdale, FL; Profile Diagnostics, Sherman Oaks, CA; and SeraCare, Oceanside, CA. The reactive HIV status of each specimen was verified using an anti-HIV reference assay. The following results were obtained using the ADVIA Centaur HIV 1/O/2 Enhanced assay:

		Number of Reactive Anti-HIV Results	
Clinical Category	*Number Tested*	*ADVIA Centaur Assay*	*Reference Assay*
Hepatitis A Infection (HAV)	10	0	0
Hepatitis B Infection (HBV)	10	0	0
Hepatitis C Infection (HCV)	10	0	0
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	10	0	0
Syphilis IgM	10	0	0
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
Toxoplasma IgM	10	0	0
Human T-cell Lymphotropic Virus (HTLV I/II)	10	0	0
Alcoholic Hepatitis	2	0	0
Multiparity	10	0	0
Flu Vaccine Recipient	10	4*	4*
Rheumatoid Arthritis (RF)	10	0	0
Anti-Nuclear Antibody (ANA)	10	0	0
Human Anti-Mouse Antibody (HAMA)	10	0	0
Crohn's Disease	10	0	0
Mixed Connective Tissue Disease (MCTD)	10	0	0
Systemic Lupus Erythematosus (SLE)	10	0	0
Ulcerative colitis	10	0	0
Elevated IgA	3	0	0
Elevated IgM	2	0	0

		Number of Reactive Anti-HIV Results	
Clinical Category	*Number Tested*	*ADVIA Centaur Assay*	*Reference Assay*
Elevated IgG	5	0	0
Graves' Disease	7	0	0
Vasculitis	10	0	0
Fibromyalgia	10	0	0
Scleroderma	10	0	0
Total Sample Tested	292	4	4

*Four flu vaccine recipient specimens reactive by ADVIA Centaur HIV 1/O/2 Enhanced assay were also reactive by the Reference assay and by HIV-1 Western blot.

Endogenous Interferents

The ADVIA Centaur HIV 1/O/2 Enhanced assay was evaluated according to CLSI Document EP7-A2 for interference due to varying levels of endogenous substances. The effects were studied up to the following concentrations: conjugated bilirubin @ 60 mg/dL, unconjugated bilirubin @ 40 mg/dL, hemoglobin @ 500 mg/dL, triglycerides @ 3000 mg/dL, cholesterol @500 mg/dL, human serum albumin @ 12 g/dL (i.e. high total protein.), high IgG @ 12 g/dL, low protein @3.5 g/dl, and biotin @500 ng/ml.
None of the interferents at the levels tested produced a change in clinical interpretation of the assay.

Serum and EDTA plasma samples positive for antibodies to HIV and spiked with high levels of conjugated bilirubin showed an increase in signal of up to 27% at 30 mg/dL and 36% at 60 mg/dL compared to unspiked controls. This effect was not observed with heparin or ACD plasma samples. There is no effect on negative specimens in any tube type. The effect of spiked conjugated bilirubin had no impact on clinical interpretation of any sample.

Serum, ACD, Li Heparin, Na Heparin and K2EDTA specimens diluted with buffer to < 3.5 mg/dl protein and spiked with antibody to HIV-1, HIV-2 or HIV-1 group O showed reduced signals up to 36% compared with spiked normal controls. Based on the results of the contrived low protein samples, high negative specimens with abnormally low protein levels should be considered for follow-up testing.

In addition, a potentially interfering effect of biotin was evaluated using the four control samples spiked with several levels of biotin. No interference was observed. An evaluation with cholesterol was performed with 10 samples in both serum and potassium EDTA plasma at 2 levels. No interference was observed.

Matrix, Collection Tube Type, Effects

The effects of collection tube type and different anticoagulants on assay performance were evaluated by testing donor specimens collected in different collection tubes containing anticoagulants shown below.

Tube Type	Material
ACD	Glass
K2 EDTA	Plastic
Sodium Heparin	Glass/Plastic
Lithium Heparin	Glass/Plastic
SST	Glass/Plastic
Serum Red Top	Glass/Plastic

Ten negative donor specimens and forty HIV-1 positive donor specimens were evaluated in the tube types listed above.

In this study there was no change in clinical interpretation when specimens in the different collection tubes were compared to specimens collected in redtop serum tubes. Negative specimens collected in sodium or lithium heparin may have elevated index values compared to serum. This could result in some high negative specimens in lithium or sodium heparin appearing reactive.

In conclusion, these collection tubes are acceptable for use with the ADVIA Centaur HIV 1/O/2 Enhanced assay.

Specimen Handling Studies

Specimens were collected in each of the matrices claimed as suitable for use in the ADVIA Centaur HIV 1/O/2 Enhanced method. These specimens were subjected to potential stresses and then tested in comparison to baseline data to determine the impact of the stress on assay accuracy using the ADVIA Centaur HIV 1/O/2 Enhanced assay. The specimen handling studies described here evaluate the effect of the following specimen handling conditions on ADVIA Centaur® HIV 1/O/2 Enhanced Index Values:

Extended time onboard the ADVIA Centaur® System
Extended time in refrigerated (2 -8°C) storage
Extended time at room temperature (25°C) storage
Extended time in freezer (–20°C) storage
Multiple freeze thaw (–20°C/2- 8°C) cycles

Specimens were collected during in-house blood draws from ten healthy donors in serum and plasma collection tubes with a variety of anti-coagulants. Specimens were spiked with HIV-1, HIV-2, or HIV-1 group O serum and aliquoted and placed in appropriate storage/stress conditions on the day of collection. Two specimens were left unspiked. A baseline Index value for each specimen was established by testing with the ADVIA Centaur HIV 1/O/2 Enhanced assay on the day of collection. All percentage recoveries were calculated against the baseline (day 0) value. Results from the specimen handling studies support the claims that specimens can be subjected to the following conditions and still generate accurate results when tested in the ADVIA Centaur HIV 1/O/2 Enhanced assay:

1. Specimens can be kept onboard the Centaur® system for at least 8 hours.
2. Specimens can be stored at room temperature for at least 24 hours
3. Specimens can be stored refrigerated (2-8ºC) up to 14 days.
4. Specimens may be stored at or below -20°C for up to 365 days with the exception of specimens collected in EDTA plastic, lithium heparin glass and plastic, and SST plastic tube types which may be stored at or below -20°C for up to 168 days.
5. Specimens can be frozen and thawed up to 6 times.

Specimen Handling - Inversion of Gel Barrier Collection tubes

A specimen handling study was done to determine if inversion of barrier gel blood collection tubes interferes with ADVIA Centaur HIV 1/O/2 Enhanced assay results. Specimens were drawn from 10 healthy in-house donors using serum and plasma (lithium heparin and potassium EDTA) gel barrier (separator) collection tubes. Specimen tubes were spiked with different amounts of anti HIV positive plasma. Three donor tubes were left unspiked. The tubes were rocked for 30 minutes, centrifuged, and an aliquot was taken. The tubes were then inverted 5 times and another aliquot was taken. The 2 aliquots were compared in the ADVIA Centaur HIV 1/O/2 Enhanced assay. A total of 5 inversions of the barrier gel collection tube had no effect on the EHIV Index Value for specimens that were spiked with anti-HIV plasma and for unspiked specimens.

On-The-Clot Specimen Storage

A study was done to determine if storing the processed serum or plasma specimen in the original collection tube ("On the Clot") rather than transferring the sample to secondary container affected the ADVIA Centaur® HIV 1/O/2 Enhanced Index Value. Fresh specimens 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 (HIV negative specimens were spiked with high positive HIV plasma before removing the aliquot). Specimens remained in the primary tubes on the clot or packed red cells and were stored at 2 – 8°C. The anti HIV activity was tested at 0, 1, 5 and 7 days. HIV antibody activity at day 0 was compared to the other time points. No negative specimens showed any significant change. Overall the positive specimens showed a change of less than 20% after 24 hours and clinical interpretation was consistent across all time points. Based on this study, specimens can be stored in the primary collection tube for up to 5 days at 2 - 8°C.

Specimen Processing – Time to Centrifugation

A study was done to determine the effect of time to centrifugation on the EHIV Index Value. Blood was drawn from eight healthy in-house donors into each of the following tube types: Serum Red Top plastic and glass, SST plastic and glass, K2-EDTA plastic, Sodium Heparin plastic and glass, Lithium Heparin plastic and glass, and ACD glass. Four donors were spiked prior to centrifugation with HIV-1, HIV-1 group O, or HIV-2 positive plasma. Each specimen was centrifuged within 2 hours of draw, 8 hours after draw, and 24 hours after draw and assayed.

The clinical status of the specimen was the same regardless of time of centrifugation or tube type. In conclusion, in comparison with immediate centrifugation, specimen processing by centrifugation up to 24 hours post draw does not result in significant changes in Index Value in the ADVIA Centaur HIV 1/O/2 Enhanced assay.

Reagent, Calibrator, and Control Real Time Stability Studies

Real-time stability studies were carried out using three lots of Centaur EHIV ReadyPack reagents, calibrators, and controls. All kits and reagents were stored at the recommended storage temperature of 2 to 8°C. Reagents, calibrators and controls were 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® HIV 1/O/2 Enhanced reagents, calibrators and controls.

Reagent Onboard Stability (OBS) Studies

Four lots of Centaur EHIV reagents have undergone reagent OBS studies on the ADVIA Centaur® system. Onboard stability testing occurred at several checkpoints after the reagents were placed onboard. A solid phase resuspension time interval of 7 days was evaluated at each OBS checkpoint. A fresh pack served as the control for each time-point. Index Value recovery within 25% or 2 standard deviations of the fresh pack defined acceptable performance. A calibration interval of 14 days was also evaluated using these results.

The on-board studies for the reagents support 28 days OBS and a 14-day recalibration for the Centaur EHIV reagents when reagents are resuspended weekly.

Reagent Shipping Stability Studies

Shipping studies for the ADVIA Centaur® HIV 1/O/2 Enhanced assay reagents indicated that the product tolerated 3 freeze/thaw/ cycles (-40°C to 2-8°C) without aggregation of the solid phase and had acceptable performance. Shipping studies also included 2-8°C to elevated temperature (30°C) cycling. Performance of EHIV ready packs cycled to elevated temperature indicated some effect of elevated temperature. The recommended shipping conditions are to ship the ReadyPack reagents in an upright position and stored at 2 to 8°C.

Calibrator and Control Open Vial Stability Studies

The calibrator and control open vial use study examined the length of time the calibrator or control was stable once the vial was opened. Open vials were stored at the recommended storage conditions of 2 to 8ºC. The open vials were sampled periodically up to 70 days post initial opening. Fresh (unopened) vials were evaluated at each time point to serve as controls. The study supports an open vial use life of up to 60 days.

Calibrator and Control Shipping Stability Studies

Shipping studies for the ADVIA Centaur® HIV 1/O/2 Enhanced assay calibrators and controls indicated that the product tolerated 3 freeze/thaw cycles (-40°C to 2-8°C and) with acceptable performance. Shipping studies also included 2-8°C to elevated temperature (30°C) cycling. Performance of EHIV calibrators and controls cycled to elevated temperature indicated some effect of elevated temperature. The recommended shipping conditions are to ship the EHIV calibrators and controls in an upright position and stored at 2 to 8°C.

Microbiology Studies

The ADVIA Centaur® HIV 1/O/2 Enhanced reagents contain 0.20% Micr-O-Protect as preservatives to protect against adventitious contamination by microorganisms. The ADVIA Centaur HIV 1/O/2 Enhanced calibrators and controls contain ProClin and Na Azide as a preservative to protect against adventitious contamination by microorganisms. The reagents and controls were challenged in a study conducted according to USP requirements for Antimicrobial Effectiveness testing to assess the ability of the reagents to withstand or control microbial contamination. Calibrators and controls have the same formulation and results for controls therefore apply to calibrators. Results indicated that the preservative systems for reagents, calibrators and controls met the USP requirements for antimicrobial effectiveness testing.

A performance microbial challenge was performed using one lot of HIV reagents and calibrators. Reagents were inoculated with two pools of microbes at 10E3 and 10E6 CFU/mL then run on the Centaur instrument. Controls were inoculated separately with seven species of microbes at 10E6 CFU/mL. Controls and in house quality control material all were within release ranges when tested using inoculated reagents at all time points. Inoculated Control Index values were consistent with the non-inoculated material. No clinically significant changes in Index values were observed after using inoculated reagents versus control [non-inoculated] reagents.

Additionally, Bayer routinely performs microbial load testing during the manufacturing of ADVIA Centaur HIV 1/O/2 reagents, calibrators and controls. The microbial load for any batch must be < 50 CFU/ml.

Instrument Studies

Environmental Testing

The purpose of environmental testing is to assess ADVIA Centaur HIV 1/O/2 Enhanced assay control recovery at the mean and extreme environmental conditions as specified. Each assay is calibrated and run on a single ADVIA Centaur® in an environmental chamber set at 18°C, 24°C and 30°C. The percent change in control recovery per degree is then calculated.

ADVIA Centaur HIV 1/O/2 Enhanced assay environmental testing data met the specification for control recovery change over the temperature range tested for specimens near the cutoff. The studies demonstrated acceptable performance of the ADVIA Centaur HIV 1/O/2 Enhanced assay when performed on instruments operating at the extremes of the temperature range for the ADVIA Centaur® system (18°C to 30°C).

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. The ADVIA Centaur HIV 1/O/2 Enhanced 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 HIV 1/O/2 Enhanced assay. The ADVIA Centaur® HIV 1/O/2 Enhanced assay is not significantly affected by any other Centaur assay sharing the same reagent probe.

Conclusions Drawn from the Non Clinical Studies

The ADVIA Centaur® HIV 1/O/2 Enhanced assay was evaluated to demonstrate performance claims for cross-reactivity, interference, matrix type, specimen handling, and reagent stability. The results of the non-clinical studies will be used in conjunction with results of the clinical trial studies to support the intended use statements of the ADVIA Centaur® HIV 1/O/2 Enhanced assay.

IX. Summary of Clinical Studies

Repeatedly Reactive Rate and Diagnostic Specificity

The repeatedly reactive rate and diagnostic specificity of the ADVIA Centaur HIV 1/O/2 Enhanced assay was determined using specimens from a population at low risk for HIV-1 or HIV-2 infection.

Specimens were collected from a total of 6060 individuals at low-risk for HIV infection. Of these 6060 specimens, 6011 were collected from healthy (normal) individuals, 24 were obtained from a prenatal population, and 25 from a hospitalized population.

Non-reactive, initially reactive, and repeatedly reactive results for the low-risk populations using the ADVIA Centaur HIV 1/O/2 Enhanced assay are shown below.

Reactivity in Low-Risk Populations

	Results Obtained with ADVIA Centaur HIV 1/O/2 Enhanced Assay				Repeatedly Reactive Specimens	
Population	Number Tested	Non-Reactive	Initially Reactive	Repeatedly Reactive	HIV-2 Immunoblot Reactive	HIV-1 Western blot Reactive
Healthy	6011	5998	13	7	1	0
Prenatal	24	23	1	1	0	1
Hospitalized	25	25	0	0	0	0
Total	6060	6046 (99.77%)	14 (0.23%)	8 (0.13%)	1 (0.016%)	1 (0.016%)

As shown in the table above, 99.77% (6046/6060) of the low risk population were initially non-reactive, 0.23% (14/6060) were initially reactive, and 0.13% (8/6060) were repeatedly reactive. Of the 8 repeatedly reactive specimens, 1 specimen from the healthy population was positive for antibodies to HIV-2 by immunoblot and 1 from the prenatal population was positive for HIV-1 by Western blot.

The diagnostic specificity of the ADVIA Centaur HIV 1/O/2 Enhanced assay was calculated as follows:

$$\text{Specificity} = \frac{\text{number of specimens in low risk population} - \text{number of repeatedly reactive specimens by ADVIA Centaur® HIV 1/O/2 Enhanced Assay}}{\text{number specimens in low risk population} - \text{number of repeatedly reactive specimens confirmed by immunoblot}} \times 100$$

Of the 6060 specimens tested, 2 were determined to be HIV-1 or HIV-2 positive by confirmatory Western blot and immunoblot testing, respectively. The results from these 2 specimens were excluded from the specificity calculation. The diagnostic specificity of the ADVIA Centaur 1/O/2 Enhanced Assay in the low risk population was 99.90% (6052/6058) with a 95% confidence interval of 99.78% to 99.96%.

Sensitivity

Reactivity and Clinical Sensitivity in Individuals Known to be Positive for Antibodies to HIV-1

The reactivity rate and clinical sensitivity of the ADVIA Centaur HIV 1/O/2 Enhanced assay was assessed in 1059 individuals who were known to be infected with HIV-1. Of the 1059 HIV-1 positive individuals, 251 individuals were symptomatic for AIDS or ARC and 808 individuals were asymptomatic for AIDS or ARC at study enrollment.

The 1059 HIV-1 positive individuals were obtained from the following geographic regions: Florida (221 specimens, 20.87%), Texas (311, 29.37%), New York (455, 42.96%), and Tennessee (72, 6.80%). The reactivity rate of the ADVIA Centaur HIV 1/O/2 Enhanced assay for HIV-1 positive individuals is shown in the table below.

	Results Obtained with ADVIA Centaur HIV 1/O/2 Assay				Licensed HIV-1/HIV-2 EIA		Repeatedly Reactive Specimens
Group	Number Tested	Non-Reactive	Initially Reactive	Repeatedly Reactive	Initially Reactive	Repeatedly Reactive	HIV-1 Western blot Reactive*
Asymptomatic	808	0	808	808	808	808	808**
Symptomatic	251	0	251	251	251	251	251
Total	1059	0 (0.00%)	1059 (100.0%)	1059 (100.0%)	1059 (100.00%)	1059 (100.00%)	1059 (100.00%)

* Five (5) specimens were found to be immunoblot positive for both HIV-1 and HIV-2.

** One (1) specimen, originally Western blot indeterminate, was subsequently determined to be HIV positive upon additional HIV-1 supplemental testing.

As shown in the table above, 100.00% (1059/1059) of the HIV-1 positive population tested were initially reactive and repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced assay.

The clinical sensitivity of the ADVIA Centaur HIV 1/O/2 Enhanced assay was 100.00% (1059/1059, 95% CI of 99.72% to 100.00%) in the HIV-1 positive population.

Reactivity in Individuals Known to be Positive for Antibodies to HIV-2

The HIV-2 positive population included 197 individuals who were known to be infected with HIV-2. Specimens from individuals infected with HIV-2 were obtained by commercial vendors from Africa and were sent to the sites for testing. The results of testing are shown in the following table

Results Obtained with ADVIA Centaur HIV 1/O/2 Enhanced Assay				Licensed HIV-1/HIV-2 EIA		Repeatedly Reactive Specimens
Number Tested	Non-Reactive	Initially Reactive	Repeatedly Reactive	Initially Reactive	Repeatedly Reactive	HIV-2 Immunoblot Reactive*
197	0 (0.00%)	197 (100.00%)	197 (100.00%)	197 (100.00%)	197 (100.00%)	197 (100.00%)

*27 (13.71%) specimens were found to be immunoblot positive for both HIV-1 and HIV-2.

As shown in the table above, 100.00% (197/197) of the HIV-2 positive population tested were initially reactive and repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced assay.

The clinical sensitivity of the ADVIA Centaur HIV 1/O/2 Enhanced assay was 100.00% (197 of 197 specimens; 95% CI of 98.49% to 100.00%) in the HIV-2 positive population.

Reactivity in Specimens Known to be Positive for Antibodies to HIV-1 Group "O"

Ten specimens from different individuals known to be positive for antibodies to HIV-1 Group "O" were tested with the ADVIA Centaur HIV 1/O/2 Enhanced Assay. All ten specimens tested were initially reactive and repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced Assay.

Reactivity in High Risk Populations for HIV-1

Individuals at high risk of HIV-1 infection included 554 prospectively enrolled individuals who had the following risk factors: intravenous drug user (IVDU), transfusion recipient, sexually transmitted diseases, renal dialysis patient, hemophilia, homosexual male and other. The reactivity of specimens from an HIV-1 high risk population is shown below.

Results Obtained with ADVIA Centaur HIV 1/O/2 Enhanced Assay				Licensed HIV-1/HIV-2 EIA			Repeatedly Reactive Specimens	
Number Tested	Non-Reactive	Initially Reactive	Repeatedly Reactive	Non-Reactive	Initially Reactive	Repeatedly Reactive	HIV-2 Immunoblot Reactive	HIV-1 Western blot Reactive
554	526 (94.95%)	28 (5.05%)	25 (4.51%)	525 (94.76%)	29 (5.23%)	29 (5.23%)	0	14 (2.53%)

All 14 specimens confirmed positive by Western blot were repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced assay (14/14 or 100% detection). Of the 554 specimens tested with the ADVIA Centaur HIV 1/O/2 Enhanced Assay, 2.04% (11/540) were repeatedly reactive but not confirmed positive by HIV-1 Western blot. Of the 554 specimens tested with the licensed HIV-1/HIV-2 EIA, 2.78% (15/540) were repeatedly reactive but not confirmed positive by HIV-1 Western blot.

Reactivity in High Risk Populations for HIV-2

Four hundred and eighty-five (485) individuals at high risk for HIV-2 infection were enrolled in this study. These individuals were considered to be at high risk for HIV-2 infection because they resided in an HIV-2 endemic area (Ivory Coast of Africa). All testing of the high-risk HIV-2 population was performed at the Bayer Diagnostics site. The reactivity of specimens from an HIV-2 high risk population is shown below.

Results Obtained with ADVIA Centaur HIV 1/O/2 Enhanced Assay				Licensed HIV-1/HIV-2 EIA			Repeatedly Reactive Specimens	
Number Tested	Non-Reactive	Initially Reactive	Repeatedly Reactive	Non-Reactive	Initially Reactive	Repeatedly Reactive	HIV-2 Immunoblot Reactive	HIV-1 Western blot Reactive
485	442 (91.13%)	43 (8.86%)	42 (8.66%)	425 (87.63%)	60 (12.37%)	42 (8.66%)	17* (3.50%)	41** (8.45%)

* 16 specimens were also HIV-1 Western blot positive and 1 was HIV-2 only

** 16 specimens that were HIV-1 Western blot positive were also HIV-2 immunoblot positive

All 17 specimens confirmed positive by immunoblot were repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced Assay (17/17, 100% detection). All 41 specimens confirmed positive by HIV-1 Western blot were repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced Assay (41/41, 100% detection). All samples that were repeatedly reactive by the ADVIA Centaur HIV 1/O/2 Enhanced Assay and the licensed HIV-1 assay were confirmed positive using either or both the HIV-1 Western blot and HIV-2 immunoblot assays.

Seroconversion Study

Twenty commercially available seroconversion panels were tested using the ADVIA Centaur® HIV 1/O/2 Enhanced assay and the reference HIV 1/2 assay. A summary of seroconversion results is presented in the following table. Not all panel members are listed below. Shown are the panel members with the first reactive result and the panel member preceding that reactive result.

ADVIA Centaur® HIV 1/O/2 Enhanced Assay
Detection of Antibodies to HIV-1 and/or HIV-2
Seroconversion Panels

Panel ID	Day of Bleed[a]	ADVIA Centaur® HIV 1/O/2 Index	ADVIA Centaur® HIV 1/O/2 Interpretation[b]	Reference HIV 1/2 S/CO	Reference HIV 1/2 Interpretation[b]
HIVSCP-001a	42	0.28	NR	0.11	NR
	47	**9.59**	**RR**	**3.80**	**RR**
PRB916	15	0.2	NR	0.07	NR
	30	**23.75**	**RR**	**10.95**	**RR**
PRB926	9	0.04	NR	0.07	NR
	27	**49.13**	**RR**	**>18.18**	**RR**
PRB929	18	0.45	NR	0.08	NR
	21	**1.36**	**RR**	0.64	NR
	25	**29.32**	**RR**	**>18.18**	**RR**
PRB931	15	0.16	NR	0.11	NR
	28	**50.01**	**RR**	**>18.18**	**RR**
PRB933	0	0.3	NR	0.09	NR
	21	**20.91**	**RR**	**>18.18**	**RR**
PRB934	0	0.34	NR	0.48	NR
	7	**5.49**	**RR**	**7.25**	**RR**
PRB935	28	0.56	NR	0.18	NR
	43	**14.2**	**RR**	**8.91**	**RR**
PRB939 (E)	23	0.11	NR	0.31	NR
	103	**43**	**RR**	**>16.95**	**RR**
PRB940	7	0.87	NR	0.19	NR
	11	**11.72**	**RR**	**2.69**	**RR**
PRB941	9	0.04	NR	0.20	NR
	18	**4.8**	**RR**	**13.52**	**RR**
PRB943	12	0.41	NR	0.16	NR
	14	0.85	NR	**1.62**	**RR**
	19	**50.01**	**RR**	**>16.95**	**RR**
PRB944	7	0.48	NR	0.19	NR
	9	**1.19**	**RR**	0.77	NR
	14	**40.25**	**RR**	**>16.95**	**RR**
PRB945	7	0.04	NR	0.17	NR
	13	**4.51**	**RR**	**3.38**	**RR**
PRB950	21	0.07	NR	0.12	NR
	28	**35.05**	**RR**	**>20.18**	**RR**

ADVIA Centaur® HIV 1/O/2 Enhanced Assay Detection of Antibodies to HIV-1 and/or HIV-2 Seroconversion Panels					
Panel ID	**Day of Bleed[a]**	**ADVIA Centaur® HIV 1/O/2 Index**	**ADVIA Centaur® HIV 1/O/2 Interpretation[b]**	**Reference HIV 1/2 S/CO**	**Reference HIV 1/2 Interpretation[b]**
PRB952	10	0.53	NR	0.17	NR
	14	**9.35**	**RR**	0.82	NR
	17	**50.01**	**RR**	**7.84**	**RR**
PRB957	16	0.53	NR	0.15	NR
	23	**10.04**	**RR**	0.94	NR
	28	**29.84**	**RR**	**13.83**	**RR**
PRB958	9	0.04	NR	0.11	NR
	15	**1.87**	**RR**	**9.56**	**RR**
PRB959	0	0.25	NR	0.18	NR
	7	**1.07**	**RR**	0.69	NR
	9	**8.87**	**RR**	**3.65**	**RR**
RP-002	63	0.31	NR	0.34	NR
	69	**2.41**	**RR**	0.57	NR
	71	**5.29**	**RR**	**2.91**	**RR**

a Day of bleed is the blood draw date minus the date of the first blood draw for the panel. The first draw date is bleed day 0

b RR = Repeatedly reactive, NR = non-reactive

Compared to the reference assay results, the first time point that was repeatedly reactive in the ADVIA Centaur® HIV 1/O/2 Enhanced assay occurred earlier in 6 panels (2 -5 days), at the same time in 13 panels, and later in 1 panel (5 days).

Overall, compared to the reference HIV assay, the ADVIA Centaur® HIV 1/O/2 Enhanced assay demonstrated efficacy for early detection of the appearance of antibodies to HIV following new HIV infection.

Genotype Study

A group of 65 worldwide specimens known to be infected with subtypes (i.e. clades) descended from the HIV-1 group M genotype were sourced from BBI (panel members from WWRB 301, 302, 303), NIBSC (National Institute for Biological Standards and Control), CDC (CDC HIV-1 Groups M and O Cameroonian Blood Bank Panel), and Hospital Carlos in Spain. The specimens were tested in the ADVIA Centaur HIV 1/O/2 Enhanced and reference HIV assays.

Results of testing in the ADVIA Centaur HIV 1/O/2 Enhanced and reference HIV assay for the HIV-1 group M genotype panel are summarized by clade in the following table:

Clade	*Number of Specimens*	*ADVIA Centaur HIV 1/O/2 Enhanced Result Number Repeatedly Reactive**
H	1	1
E	2	2
F	1	1
A, E	1	1
A, F	1	1
A, G	4	4
D	1	1
F	1	1
F	2	2
G	2	2
A	6	6
C	7	7
D	5	5
E	3	3
G	3	3
A	1	1
A, C	1	1
A, G	1	1
B, A	1	1
B	4	4
B, C	1	1
B, D	1	1
B, F	1	1
B, F	1	1
C, A	2	2
C	2	2
D, A	1	1
D	2	2
E, A	1	1
E, B	1	1
E, C, A	1	1
E, F, B	1	1
F, B	1	1
F	1	1

* All specimens repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced Assay were repeatedly reactive in the Reference HIV 1/2 assay.

Samples from 65 specimens (100.00%) in the HIV-1 group M genotype panel were reactive in the ADVIA Centaur HIV 1/O/2 Enhanced and reference HIV assays. The following clades from the HIV-1 group M genotype were detected: A, B, C, D, E, F, G, and H.

The ADVIA Centaur HIV 1/O/2 Enhanced and reference assays detected HIV infection in samples from 10 of 10 patients (100%) who were infected with the HIV-1 group O genotype.

System Reproducibility

The precision of the ADVIA Centaur® HIV 1/O/2 Enhanced assay was tested at 3 testing sites using a 12-member panel and 3 reagent lots. The 12-member panel included 5 dilutions of a specimen containing antibodies to HIV-1, 5 dilutions of a specimen containing antibodies to HIV-2, and 2 undiluted HIV-nonreactive specimens. Also tested were positive controls for HIV-1, HIV-1 group O, and HIV-2; and a negative control for HIV-1/O/2. The 12-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).

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® HIV 1/O/2 Assay
System Reproducibility
All Testing Sites and Reagent Lots

Panel Member	Mean ADVIA Centaur® HIV Index Value	Within Run[a]		Between Run[b]		Between Testing Site[c]		Between Lot[d]		Total[e]		Number of Observations
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	
HIV-1 high negative	0.94	0.081	8.60	0.050	5.32	0.081	8.64	0.029	3.09	0.128	13.65	270
HIV-1 low positive	5.07	0.218	4.30	0.213	4.20	0.290	5.73	0.067	1.32	0.426	8.40	270
HIV-1 high positive	12.06	0.474	3.93	0.582	4.83	0.799	6.63	0.439	3.64	1.181	9.80	270
HIV-2 high negative	0.89	0.129	14.46	0.116	12.99	0.064	7.21	0.044	4.91	0.190	21.30	267*
HIV-2 low positive	5.20	0.267	5.13	0.173	3.33	0.234	4.50	0.285	5.48	0.487	9.37	269*
HIV-2 high positive	12.07	0.471	3.90	0.485	4.02	0.822	6.81	0.669	5.55	1.257	10.42	270
Negative	0.29	0.071	NA	0.039	NA	0.072	NA	0.084	NA	0.138	NA	270
HIV-1 Group “O” low positive	4.52	0.377	8.35	0.190	4.20	0.255	5.64	0.918	20.31	1.042	23.06	270
HIV-1 Group “O” high positive	11.04	0.981	8.88	0.434	3.93	0.731	6.62	2.173	19.69	2.531	22.93	270
HIV-1 high positive	18.54	0.805	4.34	0.918	4.95	1.405	7.58	0.322	1.74	1.889	10.19	270
HIV-2 high positive	18.40	0.806	4.38	0.921	5.01	1.525	8.29	0.997	5.41	2.195	11.93	270
Negative	0.29	0.080	NA	0.047	NA	0.075	NA	0.095	NA	0.153	NA	270
HIV-1/O/2 Negative Control	0.22	0.053	NA	0.049	NA	0.089	NA	0.084	NA	0.142	NA	265*
HIV-1 Positive Control	3.20	0.143	4.47	0.080	2.50	0.135	4.22	0.041	1.29	0.216	6.76	270
HIV-2 Positive Control	5.62	0.250	4.44	0.201	3.58	0.232	4.12	1.255	22.31	1.316	23.39	270
HIV-1 Group “O” Positive Control	3.61	0.263	7.27	0.125	3.47	0.078	2.17	0.204	5.64	0.364	10.07	270

NA = Not applicable

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

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.

* Outliers, defined as values outside the range of 5.5 SD per panel member were not included in this analysis. Outliers were identified for HIV-2 high negative panel (3 replicates), HIV-2 low positive panel (1 replicate), and the HIV-1/O/2 negative control (2 replicates) in the calculation of precision and reproducibility estimates for one lot at one testing site.

X. Conclusions Drawn from the Studies

Multicentered clinical studies were conducted in the US. The ADVIA Centaur® HIV 1/O/2 assay performed with clinical sensitivity and specificity comparable to current commercially available licensed assays.

- The diagnostic specificity of the ADVIA Centaur® HIV 1/O/2 Enhanced Assay was 99.90% (6052/6058; 95% CI of 99.78% to 99.96%) (normal blood donors, prenatal and hospitalized individuals).
- The clinical sensitivities of the ADVIA Centaur® HIV 1/O/2 Enhanced Assay were 100.00% (1059/1059; 95% CI of 99.72% to 100.00%) in the HIV-1 positive population (HIV-1 positive individuals who were symptomatic or asymptomatic for AIDS or ARC,) and 100.00% (197/197; 95% CI of 98.49% to 100%) in the HIV-2 positive population,
- Reactivity in the HIV-1 high risk population by ADVIA Centaur® HIV 1/O/2 Enhanced Assay showed 100% detection (14/14) among the specimens that were confirmed positive by Western blot. Reactivity in the HIV-2 high risk population showed 100% detection (17/17) among specimens that were confirmed positive by immunoblot, and 100% detection (41/41) in all 41 specimens confirmed positive by HIV-1 Western blot. These data indicate that no false negative results were noted in the ADVIA Centaur® HIV 1/O/2 Enhanced Assay.
- The ability of the ADVIA Centaur® HIV 1/O/2 Enhanced Assay to detect the appearance of HIV infections was demonstrated with the seroconversion panel evaluation. Compared to the reference assay results, the first time point that was repeatedly reactive in the ADVIA Centaur® HIV 1/O/2 Enhanced Assay and that was confirmed positive by supplemental testing, occurred earlier in 6 panels, at the same time in 13 panels, and later in 1 panel. Overall, the ADVIA Centaur® HIV 1/O/2 Enhanced Assay demonstrated efficacy in detecting the appearance of antibodies to HIV following HIV infection.
- Results of an evaluation of well characterized specimens from patients infected with HIV-1 group M genotype (subtypes A through H) showed that the ADVIA Centaur® EHIV 1/O/2 assay detected HIV infection in samples from 65 of 65 patients (100.00%) who were infected with the HIV-1 group M genotype. Also, the ADVIA Centaur® EHIV 1/O/2 assay detected HIV infection in well characterized samples from 10 of 10 patients (100.00%) who were infected with the HIV-1 group O genotype.
- Precision and reproducibility of the ADVIA Centaur® HIV 1/O/2 Enhanced Assay were good with minor variability from run to run, day to day, or reagent lot to reagent lot.

The results from both the non-clinical and clinical studies indicate that the ADVIA Centaur® HIV 1/O/2 Enhanced Assay, together with supplemental testing, can be used safely and effectively for the qualitative in vitro determination of antibodies to HIV in human serum and plasma.

Risk/benefit Analysis

As a diagnostic test, the ADVIA Centaur® HIV 1/O/2 Enhanced 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 HIV-1 or HIV-2 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.

Safety

Based on the results of the non-clinical and clinical laboratory studies, the ADVIA Centaur HIV 1/O/2 Enhanced assay, when used according to the provided directions and in conjunction with other serological and clinical information, should be safe and effective and pose minimal risk to the patient due to false test results.

Effectiveness

The effectiveness of the ADVIA Centaur® HIV 1/O/2 Enhanced assay has been demonstrated for use in determining if antibodies to HIV virus are present in an individual's serum or plasma. A reasonable determination of the effectiveness of the ADVIA Centaur® HIV 1/O/2 Enhanced assay as an aid in the diagnosis of HIV infection has been demonstrated.

XI. Panel Recommendations

XII. FDA Decision

XIII. Approval Specifications

Directions for Use:	Refer to labeling
Hazards to Health from Use of the Device:	Refer to Precautions and Warnings and Limitations statements contained in the labeling.
Post-approval Requirements and Restrictions:	Refer to Approval Order