SUMMARY OF SAFETY AND EFFECTIVENESS

Product: Bio-Rad Geenius™ HIV 1/2 Supplemental Assay

I. General Information

Device Generic Name: HIV Detection Test

Device Trade Name: Geenius™ HIV 1/2 Supplemental Assay

Device Product Code:

Applicant's Name and Address: Bio-Rad Laboratories
6565 185th Avenue NE
Redmond, WA 98052
Phone: 425-881-8300
Fax: 425-498-1651

Premarket Approval Application (PMA) Number: BP 140120

Date of Panel Recommendation: Not Applicable

Office's Signatory Authority: Jay S. Epstein, M.D.
Director, OBRR/CBER

□ **I concur with the summary review.**

□ **I concur with the summary review and include a separate review to add further analysis.**

□ **I do not concur with the summary review and include a separate review.**

Date of Notice of Approval to the Applicant:

Material Reviewed/Consulted: The PMA, amendments to the PMA, and other specific documentation used in developing the Summary of Safety and Effectiveness (SSE)

Review memos from the following reviewers were used in developing the SSE:

Discipline reviewed	Reviewer names
Clinical and Non-clinical/Analytical	Pradip Akolkar Uros Djekic
Product Design	Pradip Akolkar
CMC	Mohan Kumar Haleyurgirisetty Krishnakumar Devadas
Instrument and Software	Diane Gubernot Babita Mahajan
Statistical	Paul Hshieh
Facility	Susan Yu
Bioresearch Monitoring	Carla Jordan
Regulatory Policy Medical Policy	Sayah Nedjar Robin Biswas

II. Intended Use

The Geenius™ HIV 1/2 Supplemental Assay is a single-use immunochromatographic assay for the confirmation and differentiation of individual antibodies to Human Immunodeficiency Virus Types 1 and 2 (HIV-1 and HIV-2) in fingerstick whole blood, venous whole blood, serum, or plasma samples (EDTA, heparin, and sodium citrate).

The Geenius™ HIV 1/2 Supplemental Assay is intended for use as an aid in the diagnosis of infection with HIV-1 and/or HIV-2. It is intended for use as an additional, more specific test to confirm the presence of antibodies to HIV-1 and/or HIV-2 for specimens found to be repeatedly reactive by diagnostic screening procedures. The assay may also be used to confirm the presence of antibodies to HIV-1 and/or HIV-2 in pediatric subjects (i.e., children as young as 2 years of age).

The results of the Geenius™ HIV 1/2 Supplemental Assay are read and interpreted only by the Geenius Reader with dedicated software.

RESTRICTIONS

- Sale of the Geenius™ HIV 1/2 Supplemental Assay is restricted to clinical laboratories that have an adequate quality assurance program, including planned systematic activities to provide adequate confidence that requirements for quality will be met and where there is assurance that operators will receive and use the instructional materials.
- The Geenius™ HIV 1/2 Supplemental Assay is approved for use only by an agent of a clinical laboratory.
- The Geenius™ HIV 1/2 Supplemental Assay is not approved for testing of specimens from blood, plasma, cell, or tissue donors that are repeatedly reactive on HIV-1/2 donor screening assays.

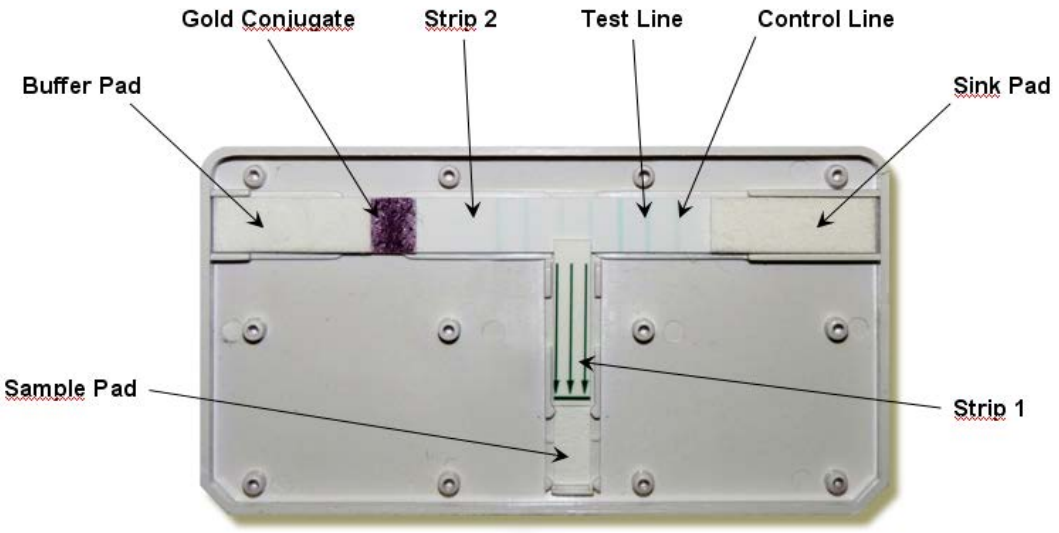
CLIA Complexity: Moderate

III. Description of the Geenius™ HIV 1/2 Supplemental Assay

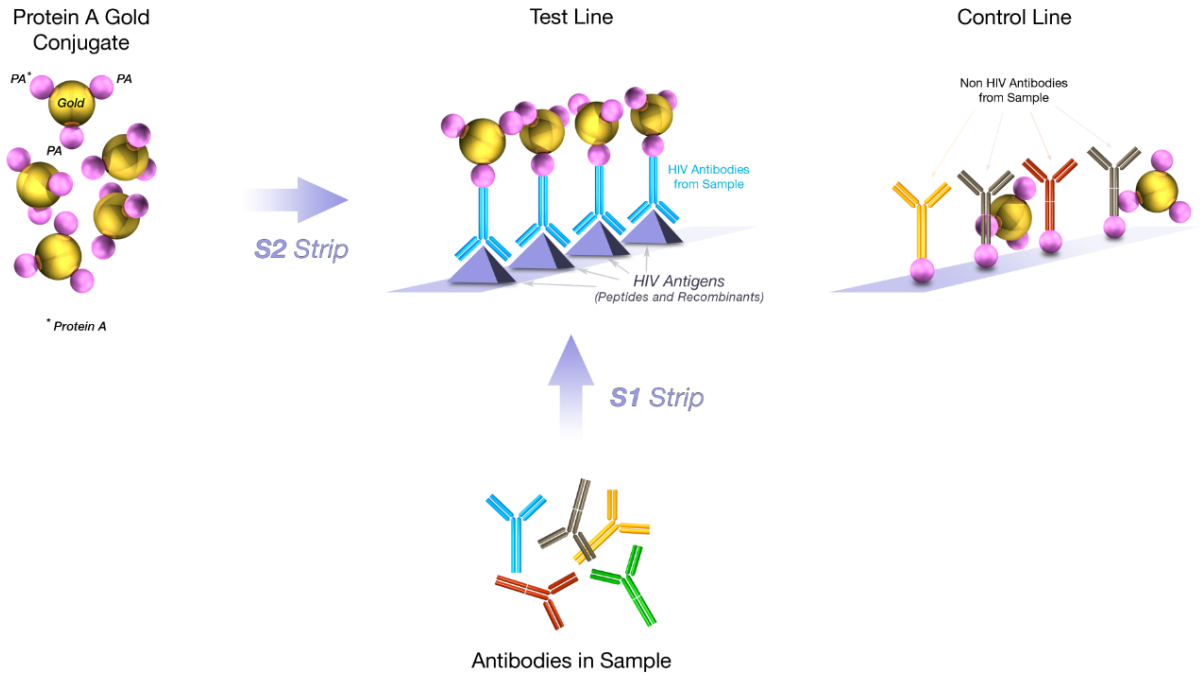
A. Device Description

The Geenius™ HIV 1/2 Supplemental Assay (REF 72461) is a rapid immunochromatographic test that incorporates highly conserved synthetic peptide sequences and recombinant proteins representing HIV-1 and HIV-2 proteins. The Geenius™ HIV 1/2 Supplemental Assay is simple and easy to use for the detection and differentiation of individual antibodies to HIV-1 and HIV-2 in serum, plasma, fingerstick whole blood, or venous whole blood.

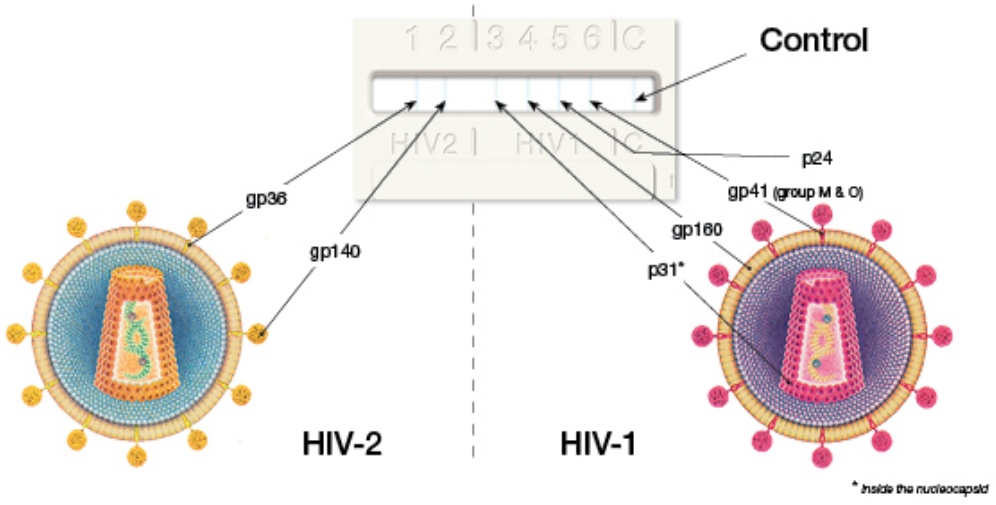
Device Design



The Geenius™ HIV 1/2 Supplemental Assay cassette (device) contains antibody-binding protein A, which is conjugated to colloidal gold dye particles, and HIV-1 and HIV-2 antigens, which are bound to the membrane solid phase ("Strip 2"). The sample is applied to the "Sample + Buffer" well. After the sample and buffer have migrated onto "Strip 1", additional buffer is added to the "Buffer" well for the protein A-gold conjugate to migrate onto Strip 2. The buffer causes the specimen and conjugate to flow laterally and facilitates the binding of antibodies in the sample to the antigens on the membrane. In a reactive sample, the antibodies are captured by the antigens immobilized in the "Test" area.



The protein A-gold conjugate binds to the captured antibodies, causing development of pink/purple lines. In the absence of HIV antibodies, there are no pink/purple lines in the Test area. The sample continues to migrate through the membrane and a pink/purple line develops in the Control (C) area, which contains protein A. This built-in procedural control provides evidence that the test was performed properly and that the sample and reagents have migrated through the cassette.



The Geenius™ HIV 1/2 Supplemental Assay contains seven (7) test lines which are numbered on the test cassette corresponding to the following antigens:

Test line 1: gp36 (HIV-2 envelope peptide), peptide mimicking the first immunodominant epitope from the gp36 region
Test line 2: gp140 (HIV-2 envelope peptides), peptide mimicking the second immunodominant epitope from the gp36 region + peptides mimicking the gp105 region
Test line 3: p31 (HIV-1 polymerase peptide), peptide mimicking the immunodominant epitope of the p31 region
Test line 4: gp160 (HIV-1 envelope recombinant protein), recombinant protein mimicking the immunodominant epitope of the gp160 region
Test line 5: p24 (HIV-1 core recombinant protein), recombinant protein mimicking the immunodominant epitope of the p24 region
Test line 6: gp41 (Groups M & O) (HIV-1 envelope peptides), peptides mimicking the immunodominant epitope of the gp41 region
Test line C: Control band (Protein A)

B. Geenius™ Reader

The Geenius Software supports the Geenius Reader. The Software runs on an external PC; the PC and the Reader are separate devices. The software allows the user to connect to the Reader. The user interacts with the software through a keyboard and a mouse. Communication between the Reader and the PC is established via a USB cable and the software graphical user interface (GUI).

The main devices controlled by the Geenius Software are LEDs, a camera, and sensors. The Geenius Software imports or generates a worklist and sets the Reader to calibrate light intensity and exposure time before it begins to run a cassette. The Software reads the cassette and collects images that are read by the Reader's camera, analyzes each image with the Picture Analyzer module for band detection, collects and analyzes the data, provides a result, and prints a report if needed. If the result is validated by the user, it can then be transmitted to the LIS and archived. The Geenius Software can also control external printers.

The operational environment for this device is a PC running under Windows 7 Pro 32 or 64 bits. The software has been developed with ----------(b)(4)----------on Windows 7 (32 and 64 bit). The following technologies are used: ----------(b)(4)----------for reporting, ----------for database management. The installation package is created using -------(b)(4)----------.

Bio-Rad provided documentation for software version 1.2, which is the version they intend to release.

C. Components of Bio-Rad Geenius™ HIV 1/2 Supplemental Assay

The **Geenius™ HIV 1/2 Supplemental Assay** contains:

Component	Description	Presentation/ Preparation
Geenius™ HIV 1/2 Test Cassette	Cassette with nitrocellulose membrane containing recombinant and synthetic HIV-1 and HIV-2 antigens in Test area, protein A in Control area, and protein A-gold conjugate in Buffer well area	20 cassettes Ready to use
Buffer	Diluent with preservative (<0.1% sodium azide, Gentamicin and Streptomycin)	5mL dropper bottle Ready to use
Microtubes, 15µL	Capillary plastic pipettes (no anti-coagulant)	20 pipettes Ready to use

Storage: the Geenius™ HIV 1/2 Supplemental Assay kit should be stored at 2 to 30°C.

The **Geenius™ HIV 1/2 Controls**, consisting of a negative control and a positive control, are intended for monitoring system performance of the Geenius™ HIV 1/2 Supplemental Assay.

The **Geenius™ HIV 1/2 Controls** (REF 72339) contains:

Component	Description	Presentation/ Preparation
Positive Control	Heat-treated human serum negative for HBsAg and anti-HCV antibodies and containing anti-HIV-1 and anti-HIV-2 antibodies. Preservative: ProClin™ 300 (0.25%), NaN3 (<0.1%)	1 vial, 120µl Ready to use
Negative Control	Human serum negative for anti-HIV-1/2 antibodies, HbsAg, and anti-HCV antibodies. Preservative: ProClin™ 300 (0.25%), NaN3 (<0.1%)	1 vial, 120µl Ready to use
Microtubes, 5µL	Capillary plastic pipettes (no anti-coagulant)	1 pkg. of 40
Positive Control Labels Card	Barcode labels for Positive Controls	1 pkg. of 20
Negative Control Labels Card	Barcode labels for Negative Controls	1 pkg. of 20

Storage: the Geenius™ HIV 1/2 Controls should be stored at 2 to 8°C.

IV. Test Procedure

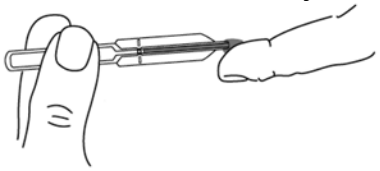
A. Specimen Collection, Preparation, and Storage

The Geenius HIV 1/2 Supplemental Assay can be performed on fingerstick or venous whole blood, serum, or plasma samples.

Fingerstick Whole Blood

Clean the finger of the person being tested with an antiseptic wipe. Allow the finger to dry thoroughly, or wipe dry with a sterile gauze pad. Using a sterile lancet, puncture the skin just off the center of the finger and wipe away the first drop with sterile gauze. Avoid squeezing the fingertip to accelerate bleeding as this may dilute the blood with excess tissue fluid. Collect 15µL from the second drop, touching the disposable Microtube pipette provided to the drop of blood until the pipette is full. Follow the procedure below.

Step 1:
Hold the 15µL Microtube horizontally and touch the blood drop with the tip. Capillary action will automatically draw the sample to the fill line and stop.



Step 2:
Fingerstick whole blood should be tested immediately after collection. To expel the sample, align the tip of the tube with the Sample + Buffer well and squeeze the bulb. If a sample won't expel, hold the tube vertically and slide a finger over the vent hole. Then align the tip with the Sample + Buffer well and squeeze the bulb.

Venous Whole Blood

Draw blood following laboratory procedure for obtaining venous blood. Collect the blood in a tube containing EDTA, heparin, or sodium citrate. Be sure the tube of blood is well mixed before sampling. Use a laboratory pipette to withdraw 15µL of the blood. Perform the test following the Assay Procedure instructions below.

DO NOT FREEZE WHOLE BLOOD. Venous whole blood specimens may be tested immediately or stored at 2°C to 8°C for up to 3 days following collection before being tested.

Serum or Plasma

Serum or plasma samples collected by standard laboratory procedure may be used in the test. The following anticoagulants may be used for collecting plasma samples: EDTA, heparin, or sodium citrate. Be sure that the tube of serum or plasma is well mixed after collection and before testing. Use a laboratory pipette to withdraw 5µL of the sample. Perform the test following the Assay Procedure instructions below.

For long-term storage, the serum and plasma specimens should be frozen (at -20°C or colder). Samples should not be used if they have incurred more than 5 freeze-thaw cycles. Mix samples thoroughly and gently after thawing, and bring to room temperature. It is also recommended to centrifuge thawed specimens to remove gross particulate matter. Serum and plasma samples may be stored at 2-8 C for up to 7 days and up to 48 hours at room temperature (18-30°C).

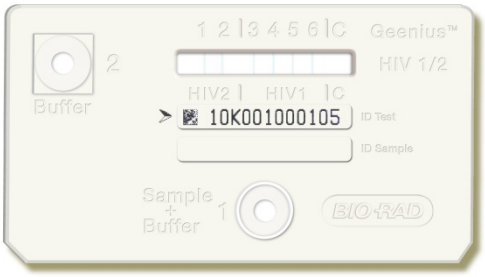
Specimen Shipping

If specimens are to be shipped, they should be packed in compliance with regulations covering the transportation of etiologic agents. Serum and plasma specimens can be shipped at ambient conditions (18-30°C) for up to 2 days or samples can be shipped refrigerated with cold packs or wet ice.

B. Assay Procedure

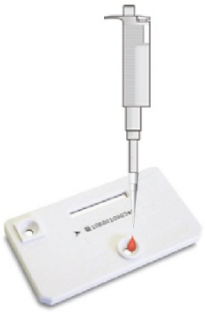
1. Remove the Geenius HIV 1/2 Supplemental Assay cassette from its pouch and place it on a flat surface. **NOTE**: Do not use the cassette if the desiccant packet is missing from the pouch; discard the cassette and open a new cassette. The desiccant does not need to be removed from the pouch. Label the cassette with sample ID or test number (see Figure 1 below). Note that the Geenius HIV 1/2 Supplemental Assay device has six (6) blue colored lines in the Test window. If any of the 6 colored lines are absent, DO NOT USE. Discard the cassette and use a new cassette.

Figure 1



2 Using a Microtube plastic pipette or laboratory pipette, dispense 5 µL of serum / plasma or 15 µL of whole blood to the center of the Sample + Buffer well 1 of the device (see Figure 2 below).

Figure 2



3 Immediately following the addition of the sample **(but no longer than 5 minutes)**, use the dropper bottle to add 2 drops or a laboratory pipette to add 60 µL of Buffer to the Sample + Buffer well 1 (see Figure 3 below).

Figure 3

4. 

Wait 5 to 7 minutes.

Wait until the blue lines in the device window completely disappear **(minimum and maximum wait times of 5-7 minutes respectively)** before going to the next step.

If some blue lines remain after 7 minutes, discard the cassette and use a new one.

NOTE: A slight bluish-greenish color may remain on the membrane, but none of the actual colored lines should be seen at this point.

Use the dropper bottle to add 5 drops or a laboratory pipette to add 150µL of Buffer to Buffer well 2 (see Figure 4 below).

Figure 4

5. 

Read the test result 15-20 minutes after adding the Buffer to Buffer well 2.

In some cases test lines may appear in less than 15 minutes; however, a minimum of 15 minutes is needed to report results.

Do not read a Geenius device with the presence of any background color. Test results must be read with the Geenius Reader. Do not read results more than 30 minutes after the addition of the Buffer to Buffer well 2.
Refer to the Geenius Reader User Manual for instructions regarding the operation of the Geenius Reader.

NOTE: Discard the used pipette tips, cassette, and any other test materials into a biohazard container.

V. Quality Control – Validation of Results

A. Internal Quality Control

Each Geenius HIV 1/2 Supplemental Assay cassette has a control line which is used to determine validity of the assay and confirm that sample has been added to the device. When the test has been performed correctly, a pink/purple line will appear in the Control (C) area to indicate the device is working properly (Refer to Interpretation of Test Results section below).

B. External Quality Control

Geenius HIV 1/2 Controls are available separately for use with the Geenius HIV 1/2 Supplemental Assay to verify the performance of the test. The Positive Control will produce a positive test result for both HIV-1 and HIV-2. The Negative Control will produce a negative test result. Run the controls as described in the Assay Procedure section for a serum or plasma sample and follow the directions in the Interpretation of Test Results section below. It is the responsibility of each facility using the Geenius HIV 1/2 Supplemental Assay to establish an adequate quality assurance program to ensure the performance of the device under specific locations and conditions of use.

Test the Geenius HIV 1/2 Controls under the following circumstances:
- When opening a new test kit lot.
- Whenever a new shipment of test kits is received.
- If the temperature of the test storage area falls outside of 2 to 30°C (36 to 86°F).

(Note that if this occurs, the Geenius HIV 1/2 Controls should be included in every test run that is performed using test kit lots that have been stored in that area).

- If the temperature of the testing area falls outside of 18 to 30°C (64 to 86°F)
- At periodic intervals as indicated by the user facility.

VI. Interpretation of Test Results

Results must be interpreted with the Geenius Reader (Ref: 72465) and the dedicated software. Refer to the Geenius Reader User Manual for instructions regarding the operation of the Geenius Reader.

The Geenius™ HIV 1/2 Supplemental Assay cassette contains a Control band (C) and six (6) test lines which are numbered on the cassette corresponding to the following:

Band 1:	gp36 (HIV-2 envelope peptide)	HIV-2 ENV
Band 2:	gp140 (HIV-2 envelope peptides)	HIV-2 ENV
Band 3:	p31 (HIV-1 polymerase peptide)	HIV-1 POL
Band 4:	gp160 (HIV-1 envelope recombinant protein)	HIV-1 ENV
Band 5:	p24 (HIV-1 core recombinant protein)	HIV-1 GAG
Band 6:	gp41 (HIV-1 Groups M and O envelope peptides)	HIV-1 ENV

Control band: Protein A

Note: A pink/purple line should always appear in the Control (C) area, whether or not a band appears in the Test area. If there is no distinct pink/purple line visible in the Control

(C) area, then the test is INVALID. A test that is INVALID cannot be interpreted. It is recommended that the test be repeated with a new cassette.

Assay Interpretation by the Geenius™ Software

The Geenius Software detects the presence or absence of Bands 1-6 above, determines the presence or absence of antibodies to HIV-1 and/or HIV-2, and generates an "HIV-1 Result" that is Positive, Indeterminate, or Negative, and an "HIV-2 Result" that is Positive, Indeterminate, or Negative. The following table indicates the criteria employed by the Geenius Software to interpret the HIV-1 Result and HIV-2 Result and provide an "Assay Interpretation."

HIV-1 RESULT	**HIV-2 RESULT**	**ASSAY INTERPRETATION by Geenius Reader Software**
Negative	Negative	**HIV NEGATIVE**
Indeterminate	Negative	**HIV-1 INDETERMINATE** [a]
Negative	Indeterminate	**HIV-2 INDETERMINATE** [b]
Indeterminate	Indeterminate	**HIV INDETERMINATE** [c]
Positive	Negative	**HIV-1 POSITIVE**
Positive	Indeterminate	**HIV-1 POSITIVE**
Negative	Positive	**HIV-2 POSITIVE**
Indeterminate	Positive	**HIV-2 POSITIVE**
Positive	Positive	**HIV-2 POSITIVE with HIV-1 cross-reactivity:** Antibody to HIV-2 confirmed in the sample. HIV-1 positivity (with only one HIV-1 envelope band, gp160 or gp41), is due to cross-reactivity and precludes confirmation of HIV-1*. *Note: Differentiation features managed by proprietary algorithm.
Positive	Positive	**HIV POSITIVE Untypeable (Undifferentiated):** Antibodies to HIV-1 and HIV-2 confirmed in the sample. This may occur in an HIV-2 positive sample with significant cross-reactivity to HIV-1, or may be due to co-infection with both HIV-1 and HIV-2 (rare)*. *Note: Differentiation features managed by proprietary algorithm.

[a] HIV-1 band(s) detected but did not meet the criteria for HIV-1 Positive
[b] HIV-2 band(s) detected but did not meet the criteria for HIV-2 Positive
[c] HIV band(s) detected but did not meet the criteria for HIV-1 Positive or HIV-2 Positive

VII. Limitations of the Test

1. The Geenius HIV 1/2 Supplemental Assay must ONLY be used with whole blood, serum or plasma. Using other types of samples or testing of venipuncture whole blood samples collected using a tube containing an anticoagulant other than EDTA, heparin, or sodium citrate may not yield accurate results. For serum samples, collect blood without anticoagulant.
2. The instructions in the package insert must be followed in order to obtain accurate results with the Geenius HIV 1/2 Supplemental Assay.
3. If results are read earlier than 15 minutes or later than 30 minutes after the addition of Buffer to Buffer well 2, the results may be erroneous.
4. The Geenius HIV 1/2 Supplemental Assay **must** be interpreted using the Geenius Reader and Software.
5. A Geenius HIV 1/2 Supplemental Assay test result that is INVALID should not be reported and the sample should be retested with a new cassette.
6. A Positive Assay Interpretation using the Geenius HIV 1/2 Supplemental Assay confirms the presence of specific antibodies to HIV-1 and/or HIV-2 in the sample. HIV and AIDS-related conditions are clinical syndromes caused by HIV-1 and HIV-2 and their diagnosis can only be established clinically.
7. False negative results may occur in individuals infected with HIV-1 and/or HIV-2 who are receiving highly active antiretroviral therapy (HAART).
8. For a positive result, the intensities of the test lines do not necessarily correlate with the titer of antibody in the sample.
9. A negative or indeterminate result does not preclude the possibility of exposure to HIV or infection with HIV. An antibody response to a recent exposure may take several months to reach detectable levels. It is recommended that testing be repeated on a specimen freshly drawn after 2-4 weeks
10. A person who has antibodies to HIV-1 or HIV-2 is presumed to be infected with the virus; however, a person who has participated in an HIV vaccine study may develop antibodies to the vaccine and may or may not be infected with HIV. It is recommended that testing be repeated on a specimen freshly drawn after 2-4 weeks.
11. Assay Interpretation limitations:
    - A Geenius HIV 1/2 Supplemental Assay cassette that contains smudges or background in the band area that may interfere with test interpretation should not

be read. The sample should be retested with a new Geenius HIV 1/2 Supplemental Assay cassette.

- An "Indeterminate" interpretation does not exclude the possibility of early seroconversion of the test subject or a cross-reaction with other retroviruses**.** The homology between HIV-1 and HIV-2 viruses can lead to cross reactivities between anti-HIV-1 and anti-HIV-2 antibodies. It is recommended that testing be repeated on a specimen freshly drawn after 2-4 weeks.
- Samples which meet the HIV-1 Positive criteria may in some rare cases show cross-reactivity on one of the HIV-2 envelope bands. In most cases, this profile that confirms an HIV-1 infection does not exclude the rare possibility of a secondary HIV-2 seroconversion (co-infection).
- Samples which meet the HIV-2 Positive criteria can show cross reactivity on one or more HIV-1 bands. In most cases, an HIV-1 indeterminate profile associated with an HIV-2 positive profile is a true "HIV-2 only" infection. However, it does not exclude the possibility of a secondary HIV-1 seroconversion (co-infection).
- Samples which meet both HIV-1 and HIV-2 Positive criteria, but are reactive with only one HIV-1 envelope band (gp160 or gp41), are generally HIV-2 positive samples which show HIV-1 cross-reactivity. This represents 54% of the cases in the clinical study of 200 samples characterized as "HIV-2 only" infections (see SENSITIVITY, section C.). Such profiles do not exclude the possibility of HIV-1 and HIV-2 co-infection, which is rare.
- Samples with reactivity to all 4 envelope bands (all of the HIV-1 env and HIV-2 env bands) have all been HIV-2 positive samples with HIV-1 reactivity that cannot be differentiated (HIV Untypeable or Undifferentiated). Such samples represent 6% of the cases in the clinical study of 200 samples that have been characterized as positive for HIV-2 only (see SENSITIVITY, section C.). Such profiles do not exclude the possibility of HIV-1 and HIV-2 co-infection, which is rare. None of the 1,043 samples from 299 patients with known HIV-1 infection were found to be HIV Untypeable or Undifferentiated (see Table 6).
- HIV-2 Indeterminate test results for samples from persons without any risk factors for HIV-2 infection should be confirmed by retesting with a new Geenius HIV 1/2 Supplemental Assay cassette before reporting.

VIII. Marketing History

This device has been marketed exclusively outside of the United States. The assay received a CE mark in March, 2013. In addition, the assay has been approved in Australia (October, 2014), Brazil (August, 2014), Croatia (July, 2013), Guatemala (August, 2013), Israel (November, 2013, provisional), Mexico (August, 2014), Saudi Arabia (June, 2014), and Ukraine (July, 2014).

IX. Potential Adverse Effects of the Device on Health

Potential adverse effects of Bio-Rad Geenius HIV 1/2 Supplemental Assay relate to the risk of false positive and false negative results. While performance studies indicate that this risk is likely to be very small, the potential for inaccurate results exists. The risk of incorrect results is minimized by following the procedures and instructions outlined in the package insert. False negative results can lead to a delay in diagnosis or treatment, and to transmission of the infection to intimate contacts of the patient. False positive results can lead to improper treatment, and adverse psychosocial consequences.

X. Summary of Preclinical Studies

A. HIV-1 Incidence / Prevalence Panel

An HIV-1 Incidence / Prevalence panel containing seven known HIV-1 positive incidence (new infections) members and eight known HIV-1 positive prevalence (long-standing infections) members was tested with the Geenius HIV 1/2 Supplemental Assay.

The Geenius HIV 1/2 Supplemental Assay was HIV-1 Positive for 100% (15/15) of the HIV-1 Incidence / Prevalence panel members with a 95% confidence interval of 79.61% - 100%.

B. HIV-1 / HIV-2 Performance Panel

An HIV-1 / HIV-2 Performance Panel containing seven HIV-1 positive and seven HIV-2 positive panel members was tested on three lots of the Geenius HIV 1/2 Supplemental Assay.

The Geenius HIV 1/2 Supplemental Assay gave correct results for the seven HIV-1 panel members ("HIV-1 Positive") and five of the HIV-2 panel members ("HIV-2 Positive") for all three lots tested. One HIV-2 panel member was HIV-2 Indeterminate on all three lots tested. Additionally, one HIV-2 panel member was HIV-2 Positive on two of three lots tested and HIV-2 Indeterminate on the remaining lot. None of the panel members was found to be Negative on any lot tested.

C. HIV-1 Group M Subtype Samples

The reactivity of the Geenius HIV 1/2 Supplemental Assay with HIV-1 Group M subtype samples was determined by testing 136 HIV-1 antibody positive Group M subtype specimens collected from individuals in Cameroon. The number of specimens of each subtype tested is as follows: A (23), A1 (1), B (1), C (1), D (4), F (6), F2 (1), G (6), A/E (2), A/G (1), H (2), J (1), K (2), U (1), and CRFs (84).

The reactivity of the Geenius HIV 1/2 Supplemental Assay for the 136 HIV-1 Group M subtype samples tested was 100% (136/136) HIV Positive, (135 HIV-1 Positive and 1 HIV Positive Untypeable/Undifferentiated), with a 95% confidence interval of 97.25% to 100%.

D. HIV-1 Group O Subtype Samples

Fifteen (15) specimens known to be positive for antibodies to HIV-1 Group O were tested with the Geenius HIV 1/2 Supplemental Assay.

The Geenius HIV 1/2 Supplemental Assay was HIV-1 Positive for 13 and HIV-1 Indeterminate for 2 of the 15 known positive HIV-1 Group O samples. None of the specimens was found to be Negative.

E. HIV-1 Seroconversion Panels

Twenty-six (26) commercially available seroconversion panels were tested with the Geenius HIV 1/2 Supplemental Assay. The reactivity of the assay with the 230 specimens in the panels is presented in Table 1.

Table 1: Reactivity in HIV-1 Seroconversion Panels

Note: The number of positive panel members found to be repeatedly reactive or positive is listed for each test.

Panel ID	Number of Panel Members Tested	HIV-1 RNA Positive Panel Members	HIV Ag/Ab Combo EIA	HIV 1/2 EIA	Geenius HIV-1/2 Supplemental Assay	Rapid HIV-1/2 Supplemental /Differentiation Test	HIV-1 Western Blot
001	9	6	6	5	3	2	3
002	13	7	5	4	2	2	3
003	10	6	5	3	2	2	2
004	8	6	3	2	0	0	0
005	7	4	5	5	5	3	4
006	8	3	2	2	0	0	0
007	3	1	1	1	1	1	1
008	14	11	5	5	3	3	2
009	6	4	4	3	2	3	2
010	10	5	3	3	1	2	0

011	27	17	16	14	14	13	13
012	25	18	17	14	13	9	11
013	6	4	3	2	2	2	2
014	5	4	5	2	1	2	0
015	8	4	4	3	1	0	0
016	6	2	2	2	1	2	0
017	6	5	4	2	2	2	2
018	9	5	4	4	4	4	1
019	8	8	7	6	5	5	1
020	6	5	4	2	1	1	0
021	6	5	3	2	0	0	0
022	4	4	3	3	0	0	1
023	6	5	4	0	1	1	2
024	7	5	2	1	1	0	0
025	7	7	7	0	4	4	4
026	6	6	5	3	2	2	2
Total	**230**	**157**	**129 / 157**	**93 / 157**	**71 / 157**	**65 / 157**	**56 / 157**
% HIV-1 RNA Positives detected			82.17%	59.24%	45.22%	41.40%	35.67%
95% Confidence Interval			75.43% - 87.36%	51.42% - 66.61%	37.64% - 53.04%	33.98% - 49.23%	28.59% - 48.43%

The Geenius HIV 1/2 Supplemental Assay results were compared to previously known results obtained with the comparator assays shown in Table 1 above**.** The HIV Ag/Ab Combo EIA, the HIV 1/2 EIA, and the Rapid HIV-1/2 supplemental/differentiation test are FDA-approved tests.

Of the 230 seroconversion panel specimens tested, 68.26 % (157/230) had detectable HIV-1 RNA. The Geenius HIV 1/2 Supplemental Assay found 45.22% (71/157, 95% CI 37.64% - 53.04%) Positive compared to 41.40% (65/157, 95% CI 33.98% - 49.23%) reactive on a Rapid HIV-1/2 supplemental/differentiation assay. This comparable result is as expected for these two similar supplemental/differentiation assays.

In this study the Geenius HIV 1/2 Supplemental Assay found 45.22% Positive compared to 35.67% (56/157, 95% CI 28.59% - 48.43%) Positive on the HIV-1 Western Blot. This result is also as expected and suggests that the Geenius assay has improved sensitivity compared to Western Blot.

XI. Summary of Clinical Studies

REPRODUCIBILITY

A 17-member reproducibility panel for the Geenius HIV 1/2 Supplemental Assay was prepared at Bio-Rad Laboratories and provided to 3 sites for testing. Three clinical lots of the Geenius HIV-1/2 Supplemental Assay were used in the evaluation.

The 17-member reproducibility panel included 5 serum members, 5 EDTA plasma members, 5 heparin plasma members and 2 Geenius HIV 1/2 Supplemental Assay controls. The reproducibility panel was tested on the Geenius HIV 1/2 Supplemental Assay according to the instructions for use. Each panel member was tested twice a day for 5 days on 3 kit lots of the Geenius HIV-1/2 Supplemental Assay, at each of 3 sites, for a total of 90 replicates per panel member at all three sites combined (5 days x 2 per day x 3 lots x 3 sites = 90 replicates per panel member). Each Geenius HIV 1/2 Supplemental Assay test result was read and interpreted using the Geenius HIV 1/2 Supplemental Assay Reader and Software.

The total percent (%) agreement of the Geenius HIV 1/2 Supplemental Assay results was calculated for each of the 17 reproducibility panel members as the number of results that were correct compared to the known sample status, along with the 95% confidence interval. Results were reported as Positive, Indeterminate, or Negative. The results are shown in Table 2. This study demonstrated that the Bio-Rad Geenius HIV 1/2 Supplemental Assay is highly reproducible.

Table 2: Reproducibility Study Results

Panel Member	Panel Member Description	Number of Replicates Correct / Number of Replicates Tested	% Agreement	95 % CI
1	HIV-1 antibody positive serum	90/90	100%	95.91% - 100%
2	HIV-1 antibody positive EDTA plasma	89/89	100%	95.86% - 100%
3	HIV-1 antibody positive heparin plasma	90/90	100%	95.91% - 100%
4	HIV-1 indeterminate serum	85/89	95.51%	89.01% - 98.24%
5	HIV-1 indeterminate EDTA plasma	84/87	96.55%	90.35% - 98.82%
6	HIV-1 indeterminate heparin plasma	85/90	94.44%	87.65% - 97.60%
7	HIV-2 indeterminate serum	80/86	93.02%	85.60% - 96.76%
8	HIV-2 indeterminate EDTA plasma	76/88	86.36%	77.66% - 92.02%
9	HIV-2 indeterminate heparin plasma	84/89	94.38%	87.51% - 97.58%
10	HIV-2 antibody positive serum	90/90	100%	95.91% - 100%
11	HIV-2 antibody positive EDTA plasma	88/90	97.78%	92.26% - 99.39%
12	HIV-2 antibody positive heparin plasma	89/89	100%	95.86% - 100%
13	HIV Negative serum	89/90	98.89%*	93.97% - 99.80%
14	HIV Negative EDTA plasma	88/90	97.78%*	92.26% - 99.39%
15	HIV Negative heparin plasma	89/90	98.89%*	93.97% - 99.80%
16	Positive control serum	90/90	100%	95.91% - 100%
17	Negative control serum	89/90	98.89%*	93.97% - 99.80%

*Discordants were due to Indeterminate results

SPECIFICITY

A. Low Risk Population Study

Four hundred and twenty (420) samples prospectively collected from 120 individuals at low risk for HIV infection (military recruits, soldiers, and civilians) were tested with the Geenius HIV 1/2 Supplemental Assay. Results are presented in Table 3.

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Table 3: Specificity of the Geenius HIV 1/2 Supplemental Assay in a Low Risk Population

Matched Sample Type	Number Tested	Geenius HIV 1/2 Supplemental Assay		
		NEG	IND	POS
Serum	120	115	5[a] (4.17%)	0
Fingerstick	60	57	3[b] (5.00%)	0
Whole Blood EDTA	58*	56	2[c] (3.45%)	0
Plasma EDTA	60	60	0	0
Whole Blood Heparin	58*	55	3[d] (5.17%)	0
Plasma Heparin	60	55	5[e] (8.33%)	0

*Two (2) whole blood EDTA and 2 whole blood heparin samples had invalid results and were excluded from analysis.

[a] Three were HIV-2 Indeterminate and two were HIV-1 Indeterminate.

[b] Two were HIV-2 Indeterminate and one was HIV-1 Indeterminate.

[c] One was HIV-2 Indeterminate and one was HIV-1 Indeterminate.

[d] One was HIV-2 Indeterminate, and two were HIV-1 Indeterminate.

[e] Three were HIV-2 Indeterminate, one was HIV-1 Indeterminate, and one was HIV Indeterminate.

The overall Indeterminate rate in the low risk population was low (18/416 = 4.33%) for all sample types combined. This low Indeterminate rate, which is much lower than the indeterminate rate for an HIV-1 Western Blot, indicates that the band intensity thresholds in the Geenius Reader are set correctly.

Note: All samples from the 120 prospective low risk subjects were non-reactive on an FDA licensed HIV-1/HIV-2 EIA test, and would not normally be tested using the Geenius HIV 1/2 Supplemental Assay.

B. False Reactive Sample Panel

A panel of 100 repository samples that were false reactive on FDA licensed or approved HIV tests were tested with the Geenius HIV 1/2 Supplemental Assay. Results are presented in Table 4.

Table 4: Specificity of the Geenius HIV 1/2 Supplemental Assay in False Reactive Samples

Assay	Number of False Reactives Tested	Geenius HIV 1/2 Supplemental Assay		
		NEG	IND	POS
HIV Ag/Ab Combo EIA	50	49	1[a] (2.00%)	0
HIV 1/2 EIA	43	40	3[b] (6.98%)	0
HIV 1/2 Rapid Test	7	5	2[c] (28.57%)	0
TOTAL	100	94	6 (6.00%)	0

[a] One combo assay false reactive sample was HIV-1 Indeterminate.
[b] Of three screening assay false reactive samples, two were HIV-1 Indeterminate and one was HIV Indeterminate.
[c] Two HIV 1/2 Rapid Test false reactive samples were HIV-1 Indeterminate.

No sample in this population tested positive on the Geenius HIV 1/2 Supplemental Assay. The overall Indeterminate rate in this population was 6% (6/100).

C. Medical Conditions Unrelated to HIV Infection

A panel of 140 repository samples representing 14 categories of medical conditions unrelated to HIV infection was tested with the Geenius HIV 1/2 Supplemental Assay. Results are presented in Table 5.

Table 5: Medical Conditions Unrelated to HIV Infection

Unrelated Medical Condition	Number Tested	Geenius HIV 1/2 Supplemental Assay		
		NEG	IND	POS
Autoimmune disease patients	10	10	0	0
Dialysis patients	10	9	1[a]	0
EBV infection	10	10	0	0
HBsAg positive	10	10	0	0
HCV infection	10	8	2[a]	0

Hemophilia patients	10	10	0	0
High Rheumatoid Factor	10	9	1[a]	0
HTLV I/II antibody positive	10	10	0	0
Multiparous (pregnant) females	10	10	0	0
Multiple transfusions	10	10	0	0
Post-Influenza vaccine recipients*	10	10	0	0
Pre-Influenza vaccine recipients *	10	10	0	0
Vaccinia vaccine recipients	10	10	0	0
Yeast (Candida) reactive	10	8	2[a]	0
TOTAL	140	(134/140) 95.71%	(6/140) 4.29%	(0/140) 0.00%

* The 10 pre-Influenza vaccine and 10 post-Influenza vaccine specimens tested in the study were matched.
[a] HIV-2 Indeterminate.

The overall indeterminate rate was 4.29% (6/140) for the unrelated medical condition samples. Of the 140 unrelated medical condition samples, 139 were negative on an FDA licensed HIV-1/HIV-2 screening assay (historical data) and one was not tested.

In a previous cross-reactivity study performed in Europe, a panel of 231 potentially cross-reactive samples representing 29 different disease states was tested on the Geenius HIV 1/2 Supplemental Assay. Of the 231 different samples, 219 specimens tested negative and 12 specimens from 10 different medical conditions tested HIV-1 or HIV-2 Indeterminate due to reactive bands at a trace level (HTLV (2/10), HCV (1/10), HAV IgG (1/10), HBs Ag (1/10), CMV IgG (1/10), Rubella IgG (1/10), RF (1/10), Scleroderma (1/2), Cirrhosis (1/5) and Malaria (2/16)). The overall indeterminate rate was 5.20% (12/231). **Note:** All of these specimens were non-reactive on an FDA licensed HIV-1/HIV-2 EIA test, and would not normally be tested using the Geenius HIV 1/2 Supplemental Assay.

D. Pediatric Sample Population

The specificity of the Geenius HIV 1/2 Supplemental Assay with pediatric samples was determined by testing ten normal pediatric samples from HIV uninfected individuals, ages 2-10 years.

Of the ten samples, nine were Negative and one was HIV-1 Indeterminate on the Geenius HIV 1/2 Supplemental Assay. The ten HIV low risk pediatric samples were negative on an FDA-approved HIV-1/2 Ag/Ab Combo EIA (historical data).

SENSITIVITY

A. HIV Positive Population

One thousand forty-three (1043) samples prospectively collected from 299 known HIV-1 positive/AIDS patients were tested with the Geenius HIV 1/2 Supplemental Assay. Results are presented in Table 6.

Table 6: Sensitivity of the Geenius HIV 1/2 Supplemental Assay in Prospective Known HIV-1 Positive / AIDS Patients

Sample Type	Number Tested	Geenius HIV 1/2 Supplemental Assay Results					Rapid HIV 1/2 Supplemental / Differentiation Test	HIV-1 Western Blot	HIV-1/HIV-2 EIA
		POS	IND	NEG	Sensitivity	95 % CI			
Serum	299	297	2[a]	0	99.33% (297/299)	97.59% - 99.82%	*99.00% (296/299)	**99.00% (296/299)	100% (299/299)
Fingerstick	148[c]	148	0	0	100% (148/148)	97.46% - 100%	NA	NA	NA
Whole Blood EDTA	150[d]	150	0	0	100% (150/150)	97.50% - 100%	NA	NA	NA
EDTA Plasma	151	150	1[b]	0	99.34% (150/151)	96.34% - 99.88%	NA	NA	NA
Whole Blood Heparin	147[e]	146	0	1[b]	99.32% (146/147)	96.24% - 99.88%	NA	NA	NA
Heparin Plasma	148[f]	147	1[b]	0	99.32% (147/148)	96.27% - 99.88%	NA	NA	NA

[a] Two AIDS patient serum samples were HIV-1 Indeterminate on the Geenius HIV 1/2 Supplemental Assay.
[b] Of the 2 AIDS patient samples that had HIV-1 Indeterminate results for serum, one had an HIV-1 Indeterminate EDTA plasma sample and the second AIDS patient had a Negative whole blood heparin sample and an HIV-1 Indeterminate heparin plasma sample.
[c] Of the 152 fingerstick samples collected, four were invalid and were excluded from the analysis. Of the 148 fingerstick results, 59 were from HIV-1 positive patients and 89 were from AIDS patients.
[d] Of the 151 whole blood EDTA samples collected, one sample was invalid and was excluded from analysis.
[e] Of the 150 whole blood Heparin samples collected, three test results were invalid and one was from a double-enrolled patient and was excluded from the analysis.
[f] Of the 150 Heparin plasma samples collected, two test results were invalid and one was from a double-enrolled patient and was excluded from the analysis.
* Three samples were indeterminate on the Rapid HIV 1/2 Supplemental / Differentiation Assay, including the two AIDS patient serum samples that were Indeterminate on the Geenius Supplemental Assay.
** Three samples were indeterminate on the HIV-1 Western blot, including the 2 AIDS patient serum samples that were HIV-1 Indeterminate the on the Geenius Supplemental Assay.

All 299 serum samples from the HIV-1 positive/AIDS patients were repeatedly reactive when tested on an FDA-licensed HIV-1/HIV-2 EIA. Three of these serum samples were HIV-1 indeterminate on both an FDA-

approved Rapid HIV-1/2 supplemental/differentiation assay and an FDA-licensed HIV-1 Western blot; therefore, the sensitivity of these two comparator assays was 99.00% (296/299) in this population.

B. CDC Stage 3 AIDS Patients

Seven hundred twenty-three (723) prospectively collected samples from 212 AIDS patients, categorized as CDC Stage 3, were tested with the Geenius HIV 1/2 Supplemental Assay. Results are presented in Table 7.

Table 7: Sensitivity of the Geenius HIV 1/2 Supplemental Assay in Prospective CDC Stage 3 AIDS Patients

Sample Type	Number Tested	Geenius HIV 1/2 Supplemental Assay					Rapid HIV-1 /2 Supp. / Diff. Test	HIV-1 Western Blot	HIV-1/HIV-2 EIA
		POS	IND	NEG	Sensitivity	95% CI			
Serum	212	210	2 [c]	0	99.06% (210/212)	96.62% - 99.74%	*98.58% (209/212)	*98.58% (209/212)	100.0% (212/212)
Fingerstick	89	89	0	0	100% (89/89)	95.85% - 100%	NA	NA	NA
Whole Blood EDTA	88 [a]	88	0	0	100% (88/88)	95.81% - 100%	NA	NA	NA
EDTA Plasma	89	88	1 [d]	0	98.88% (88/89)	93.90% - 99.80%	NA	NA	NA
Whole Blood Heparin	122[b]	121	0	1 [d]	99.18% (121/122)	95.50% - 99.86%	NA	NA	NA
Heparin Plasma	123[e]	122	1 [d]	0	99.19% (122/123)	95.53% - 99.86%	NA	NA	NA

[a] Of 89 whole blood EDTA samples collected, one test result was invalid and was excluded.

b Of 124 whole blood heparin samples collected, one test result was invalid and one was from a double-enrolled patient and was excluded from the analysis

[c] Two samples were HIV-1 Indeterminate.

[d] Of the two patient samples that had HIV-1 Indeterminate results for serum, one had an HIV-1 Indeterminate EDTA plasma sample. The second had a Negative whole blood heparin sample and an HIV-1 Indeterminate heparin plasma sample.

e Of 124 heparin plasma samples collected, one was from a double-enrolled patient and was excluded from the analysis.

* Three samples were indeterminate on both the Rapid HIV 1/2 Supplemental Differentiation Assay and the HIV-1 Western Blot, including the two samples that were indeterminate on the Geenius Supplemental Assay.

Two CDC Stage 3 AIDS patients (diagnosed in 2002 and 2004, respectively) had Indeterminate results on the Geenius HIV 1/2 Supplemental Assay.

All 212 serum samples from the AIDS patients were repeatedly reactive when tested on an FDA-licensed HIV-1/HIV-2 EIA. Two samples were HIV-1 indeterminate on both an FDA-approved Rapid HIV-1/2 supplemental/differentiation assay and an FDA-licensed HIV-1 Western Blot; therefore, the sensitivity of these two comparator assays in this population was 98.58% (209/212).

C. HIV-2 Positive Specimens

Two hundred (200) known HIV-2 antibody positive specimens obtained from individuals from different geographic locations (161 from Ivory Coast, 20 from Guinea Bissau, and 19 from the USA) were tested with the Geenius HIV 1/2 Supplemental Assay.

Of the 200 known HIV-2 antibody positive specimens, 77/200 = 38.5% were interpreted as HIV-2 Positive, 108/200 = 54% were interpreted as HIV-2 Positive with HIV-1 cross-reactivity, 12/200 = 6.0% were HIV Untypeable (Undifferentiated), and 3/200 = 1.5% were HIV-2 Indeterminate. None of the specimens was found to be Negative.

All samples from the 200 known HIV-2 positive individuals were repeatedly reactive on an FDA-licensed HIV-1/HIV-2 EIA test (historical data).

D. Pediatric Sample Population

The reactivity of the Geenius HIV 1/2 Supplemental Assay in HIV-1 positive pediatric patients was determined by testing 40 HIV-1 antibody positive pediatric samples from individuals ages 2-20. The number of specimens of each pediatric age group tested is as follows: ages 2-5 (2), ages 6-10 (8), ages 11-15 (10), and ages 16-20 (20).

The reactivity of the Geenius HIV 1/2 Supplemental Assay with the HIV-1 positive pediatric samples was 100% HIV-1 Positive (40/40), with a 95% CI of 91.22% to 100%. The 40 HIV-1 positive pediatric samples were all repeatedly reactive on an FDA-approved HIV 1/2 Ag/Ab Combo EIA and positive on an HIV-1 Western Blot (historical data).

XII. Inspections

A. Manufacturing facility

A February 2014 FDA Level 2 Quality System Inspection of the ------(b)(4)------ facility and an April 2014 TeamBio inspection of the Redmond, Washington facilities were classified as Voluntary Action Indicated (VAI). Based on the inspection history of the manufacturing facilities, the pre-approval inspection for this PMA was waived.

B. Bioresearch Monitoring (BIMO) Inspections

CBER Bioresearch Monitoring (BIMO) issued high-priority inspection assignments at three of four testing sites in the United States. These inspections did not reveal significant problems that impact the data submitted in this PMA. The inspections were classified as No Action Indicated (NAI).

XIII. Conclusions Drawn from the Studies

A. Risk/Benefit Analysis

The Geenius™ HIV 1/2 Supplemental Assay provides useful information to the patient and to the healthcare provider on the HIV status of an individual. It has the potential, as a rapid test, to reduce delays to confirmation of HIV antibody positivity, counseling, and treatment. This is expected to be helpful in preventing the transmission of HIV infection, and may be beneficial to patients and public health authorities conducting surveillance initiatives.

Risks associated with a rapid HIV supplemental assay relate primarily to its rates of false negative, false positive, and indeterminate results. Performance studies have demonstrated that the Geenius HIV 1/2 Supplemental Assay has a high level of sensitivity and specificity. The rate of indeterminate results with the Geenius HIV 1/2 Supplemental Assay is very low.

Overall, the information provided by Bio-Rad indicates that the benefits of the Geenius HIV 1/2 Supplemental Assay outweigh the risks associated with its use.

B. Safety and Effectiveness

Performance studies showed that the overall rate of indeterminate results for the Geenius HIV 1/2 Supplemental Assay for all specimen types studied (fingerstick whole blood, venous whole blood, serum, and plasma) is very low. The Geenius HIV 1/2 Supplemental Assay has high sensitivity and specificity for all specimen types studied, resulting in fewer Indeterminate test results for specimens that are repeatedly reactive on a diagnostic screening assay compared to an HIV-1 Western Blot.