Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

1. GENERAL INFORMATION

Device Generic Name:	Rapid Test for HIV 1/2 Antibody and *Treponema pallidum* Antibodies
Device Trade Name:	DPP® HIV-Syphilis System
Device Product Code:	**HIV:** MZF **Syphilis:** LIP
Applicant Name and Address:	Chembio Diagnostic Systems, Inc. 3661 Horseblock Road Medford, NY 11763
Establishment Registration Number:	2431980
Premarket Approval Application (PMA) Number:	BP 180191
Date of Panel Recommendation:	Not applicable

□ **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.**

Office's Signatory Authority:	Anne Eder, M.D Acting Director OBRR/CBER
Date of FDA Notice of Approval:	October 02, 2020

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
Scientific Lead	Pawan K. Jain
Clinical	Pawan K. Jain Nicholas Anderson
Non-clinical/Analytical	Krishnakumar Devadas
Product Design	Pawan K. Jain Krishnakumar Devadas
Instrument and Software	Nicholas Anderson
CMC	Pawan K. Jain Mohan Kumar
DMPQ	Joyce Rockwall
Statistical	Tie-Hua, Ng
CDRH (Syphilis part of the device)	Kristy Bialas Ryan Karsner Stefanie Akselrod
Bioresearch Monitoring	Bhanu Kannan
Labeling and Promotional Advertising	Dana Jones
Scientific and Programmatic Aspects	Pradip Akolkar David Leiby Julia Lathrop Indira Hewlett

2. INTENDED USE

The DPP® HIV-Syphilis System is a single-use rapid, qualitative, multiplex, immunoassay for the detection of antibodies to Human Immunodeficiency Virus Types 1 and 2 (HIV-1/2), and/or *Treponema pallidum* bacteria (the causative agent of syphilis) in fingerstick whole blood, potassium-EDTA venous whole blood or potassium-EDTA plasma specimens. The test is intended to be used with the DPP Micro Reader. The test is intended for use by trained professionals in point of care and laboratory settings to aid in the diagnosis of HIV and syphilis infection.

This test is suitable for use in multi-test algorithms designed for the statistical validation of rapid HIV test results and when multiple rapid HIV tests are available.

The test is intended to be used as the first-tier assay in the reverse sequence syphilis screening algorithm to aid in the detection of infection with *T. pallidum*. A diagnosis of syphilis must be made in the context of treponemal and non-treponemal test results and in conjunction with clinical findings. This test is not intended for use as a confirmatory test in the “reverse sequence syphilis screening algorithm.”

The results of DPP HIV-Syphilis test are read and interpreted only by DPP Micro Reader with dedicated software.

The test is not intended for use in screening blood, blood products, or human cells or tissue or cellular and tissue-based products (HCT/Ps) for HIV and Syphilis.

RESTRICTIONS

- Sale of the DPP HIV-Syphilis System is restricted to clinical laboratories that have an adequate quality assurance program including planned activities to provide adequate confidence that requirements for quality will be met; and
- Where there is assurance that operators will receive and use instructional materials.
- The DPP HIV-Syphilis System is approved for use only by an agent of a clinical laboratory.
- Test subjects must receive the “Subject Information” brochure, prior to specimen collection and appropriate counseling when test results are provided.
- The DPP HIV-Syphilis System is not approved for use to screen donors of blood, plasma, cells, or tissue.

3. DEVICE DESCRIPTION

The DPP HIV-Syphilis System employs Chembio's patented DPP (Dual Path Platform) technology and consists of a sample path and a reagent path, which intersect in the antibody detection (test and control) zones in the readout window of the test cassette. A specimen is collected and applied to the SAMPLE+BUFFER Well #1 of the DPP test cassette to initiate the test. The sample flows along the sample path membrane and is delivered to the test zone of the reagent strip, where specific HIV antigens (Test Line 1), a *T. pallidum* recombinant antigen (Test Line 2), and Protein A (Control Line) are immobilized. Antibodies to HIV and/or *T. pallidum*, if present in the sample, bind instantly to the immobilized HIV and/or *T. pallidum* antigens in the TEST area, while non-specific IgG binds to the Protein A in the CONTROL area. The dissolution of the soluble TEST and CONTROL lines indicates successful sample application. Five minutes after adding the sample, DPP Running Buffer is added to the BUFFER Well #2. The buffer releases the antibody-binding colored conjugate, which migrates to the TEST and CONTROL Line area. A DPP Micro Reader is used to interpret test results between 10 and 25 minutes after Running Buffer is added to BUFFER Well #2.

4. COMPONENTS OF THE DPP HIV-SYPHILIS SYSTEM

4.1 Each Kit Contains the Following Items to Perform 20 Tests:

- 20 Individually Pouched DPP HIV-Syphilis Test Devices, each containing:
  - 1 DPP HIV-Syphilis Test Device
  - 1 Desiccant Pouch
- 20 Disposable 10 µL Sample Loops with Break Point - BLUE

- 20 DPP SampleTainer® Bottle - BLACK Cap
  1ml, contains (b) (4) phosphate, sodium chloride, EDTA, Tween 20, avidin, and chicken serum, and (b) (4) and sodium azide as preservative.
- 1 DPP Running Buffer - GREEN Cap 6 ml contains (b) (4) phosphate, sodium chloride, EDTA, Tween 20, avidin, chicken serum, and urea, and (b) (4) and sodium azide as preservative
- 1 Product Insert for the DPP HIV-Syphilis system

4.2 Accessories Required but Supplied Separately

4.2.1 DPP HIV-Syphilis Rapid Test Control Pack (Catalog #65-9555-0)

Each package contains:

- 1 HIV-1 Reactive Control (0.5 ml)
  - Heat inactivated human plasma positive for antibodies to HIV-1, diluted in normal human plasma; negative for Hepatitis B surface antigen, Hepatitis C antibody and HTLV I/II antibodies
- 1 HIV-2 Reactive Control (0.5 ml)
  - Heat inactivated human plasma positive for antibodies to HIV-2, diluted in normal human plasma; negative for Hepatitis B surface antigen, Hepatitis C antibody and HTLV I/II antibodies.
- 1 *Treponema pallidum* Reactive Control (0.5 ml)
  - Human plasma positive for treponemal antibodies to *T. pallidum*, diluted in stabilizing matrix containing normal human plasma; negative for Hepatitis B surface antigen, Hepatitis C antibody and HTLV I/II antibodies.
- 1 Nonreactive Control (0.5 ml)
  - Normal human plasma; negative for antibodies to HIV-1, HIV-2 and *T. pallidum*.; negative for Hepatitis B surface antigen, Hepatitis C antibody and HTLV I/II antibodies.
- 1 Product Insert for the DPP HIV-Syphilis Rapid Test Control Pack

4.2.2 DPP Micro Reader

Each kit contains:

- 1 DPP Micro Reader configured for use in the DPP HIV-Syphilis System
- 3 Lithium-ion, type CR2032 (3 V/230 mAh), coin cell batteries (installed)
- 1 DPP Cartridge Adapter
- 1 USB Power Adapter (5V/1000 mA)

4.3 Materials Required but Not Provided

- Clock, watch, or other timing device

- Pipettor capable of delivering 10 µL of sample may be used in lieu of the disposable 10 µL sample loop supplied with the Kit (for venous whole blood or plasma specimens)
- Disposable gloves
- Sterile gauze (for fingerstick whole blood specimens)
- Antiseptic wipes
- Biohazard disposal container
- Sterile Safety Lancet (for fingerstick whole blood specimens)
- Collection devices (for venous whole blood or plasma specimens)

5. INSTRUMENTATION AND SOFTWARE

The DPP Micro Reader is intended for use with the DPP HIV-Syphilis System. It is a portable, battery powered instrument that uses assay-specific algorithms to analyze the test and control line reflectance to determine the presence or absence of antibodies to HIV and/or *Treponema pallidum* in a patient sample (venous whole blood, fingerstick whole blood or plasma). The DPP Micro Reader verifies the presence of the control line and measures color intensity at each of the two test line positions; it interprets the test results using an algorithm including assay-specific cut-off values, and displays a Reactive ("R"), Non-reactive ("NR") or invalid ("INV") result on an LCD Panel for HIV and Syphilis (*T. pallidum*) after approximately 3 seconds. The DPP Micro Reader is designed by opTricon Gmbh and customized per Chembio User Requirements Specifications.

The DPP Micro Reader utilizes an Electrically Erasable Programmable Read Only Memory (EEPROM) firmware program, which provides a standard operating environment for the assay specific software. The EEPROM firmware stores the settings utilized to run the assay specific software, which is loaded whenever the DPP Micro Reader is powered on, i.e. no memory storage when the device is powered down. The design and quality control of the DPP Micro Reader and assay specific firmware and software are maintained and controlled by opTricon Gmbh, in accordance with the requirements set forth by Chembio Diagnostic Systems, Inc.

The DPP Micro Reader is a stand-alone instrument. It does not have interfaces with external devices except for the USB power cord, which is used to upload the test specific software at Chembio. The same USB power cord is used as an alternative power source by the end user and is not intended for or capable of data transfer.

6. TEST PROCEDURE

6.1. Specimen Collection, Preparation and Storage

- Prior to specimen collection, provide test subjects with Subject Information Notice and pre-test counseling according to CDC Guidelines for Rapid HIV Testing

- The DPP HIV-Syphilis System can be performed on fingerstick whole blood, potassium-EDTA venous whole blood or potassium-EDTA plasma samples.

6.2. Storage and Handling of DPP HIV-Syphilis System

- The DPP HIV-Syphilis Test Devices should be stored in unopened pouches at 2 to 30°C (36 to 86°F).
- Do not freeze the test kit components.
- Do not open pouch until you are ready to perform a test.
- When stored as indicated, test devices are stable until the expiration date marked on the pouch.
- Both Running Buffer and DPP SampleTainer Bottles should be stored at 2 to 30°C (36 to 86°F) in their original containers
- If specimens are to be shipped, they should be packed in compliance with regulations covering the transportation of etiologic agents. Potassium-EDTA venous whole blood and potassium-EDTA plasma specimens should be shipped refrigerated with cold packs or wet ice

6.3 Running the DPP HIV-Syphilis System

- All components for the DPP HIV-Syphilis System are ready to use as supplied. If the sample and/or kit components have been refrigerated, remove them from the refrigerator and allow them to come to a temperature of 18 to 30° C (64 to 86°F) prior to testing.
- Remove the DPP HIV-Syphilis Test Device from its pouch and place it on a flat surface (it is not necessary to remove the Desiccant Packet from the pouch).
- Label the Test Device with patient ID or identification number
- The DPP HIV-Syphilis Test Device has 3 colored lines in Test Window; the 2 test lines are blue, and the control line is green
- Remove (unscrew) the DPP SampleTainer Bottle BLACK CAP keeping the WHITE CAP with the dropper tip screwed onto the bottle
- Invert the DPP SampleTainer Bottle (BLACK CAP), containing the collected sample, and hold it vertically (not at an angle) over the SAMPLE + BUFFER Well 1.
- Add 2 drops (~65µL) slowly, dropwise, into the SAMPLE + BUFFER Well 1
- **Wait 5 minutes.** The blue and green colored lines should have disappeared from the rectangular Results window
- Invert the Running Buffer bottle (GREEN CAP) and hold it vertically (not at an angle) over BUFFER Well 2. Add 4 drops (~135µL) of Buffer (GREEN cap) slowly, dropwise, into BUFFER Well 2.
- For Fingerstick, Potassium-EDTA Venous Whole Blood, or Potassium-EDTA Plasma

Test Results can be read using the DPP Micro Reader between 10 and 25 minutes after the addition of the Running Buffer to BUFFER Well 2 using the DPP Micro Reader

6.4 Using the DPP Micro Reader

- Place the DPP Test Device Holder on a flat surface. Match the Reader with the DPP Test Device Holder by inserting the base of the Reader so that the “slanted edge” meets the corresponding “slanted corner” in the Test Device Holder socket.
- Connect the DPP Micro Reader to the supplied Test Device Holder as shown below. The DPP Micro Reader is secure in the DPP Test Device Holder once a “clicking” sound is heard
- At the time indicated for reading the test results, place the DPP Micro Reader and Test Device Holder on top of the Test Device and press the button. The DPP Micro Reader will go through the start-up process
- Self-check shows all the display and the number of available tests
- When display shows RDY; it is ready for use
- Press the button again and the DPP Micro Reader will show “RUN
- After a few seconds, results for HIV and for *Treponema pallidum* will be displayed one after the other.

6.5 Procedural Notes

- If Desiccant Packet is missing, DO NOT USE, discard Test Device and start a new test
- If the DPP HIV-Syphilis Test Device 3 colored lines are absent, DO NOT USE, discard Test Device and a new Test Device
- The blue and green colored lines should have disappeared from the rectangular Results window. If not, DO NOT USE, discard test device and repeat the procedure with a new DPP test device.
- Do not attempt to interpret the results visually. The DPP micro reader should always be used to obtain the results.
- Discard the used Sample Loop, Test Device, and any other test materials into a biohazard waste container.
- When using the DPP microreader, check to make sure that the window at the bottom of the reader is clean of finger marks and dust or lint before using the reader
- The Reader and Test Device Holder assembly must be on top of the Test Device when reading the device for results to be valid.
- Results will be displayed for approximately 50 seconds before the DPP Micro Reader shuts-off.

7. RESULTS

7.1 Calculation

Not Applicable for this device.

7.2 Quality Control Procedures

Built-in Control Feature

The control line serves as a built-in internal control and gives confirmation of sample addition and proper test performance. The DPP Micro Reader verifies the presence of the control line and measures color intensity at each of the test line positions; it interprets the results using an algorithm including assay-specific cut-off values, and reports a reactive, nonreactive or invalid result after approximately 3 seconds. (Please see: Interpretation of Test Results).

External Quality Control

The DPP HIV-Syphilis Rapid Test Control Pack containing Reactive/Nonreactive Controls (Catalog #: 60-9555-0) are available separately for use with the DPP HIV Syphilis System. The Controls are used to verify the operator's ability to properly perform the test and to interpret the results.

The HIV-1/Syphilis Reactive Control will produce an HIV and Syphilis reactive test result when read using the DPP Micro Reader. The HIV-2 Reactive Control will produce an HIV reactive and Syphilis nonreactive test result when read using the DPP Micro Reader. The Nonreactive Control will produce a nonreactive test result for HIV and Syphilis when read using the DPP Micro Reader. Run the controls as described in the Test Procedure section for a plasma sample and follow the directions in the Interpretation of Results section of this product insert. It is the responsibility of each facility using the DPP HIV-Syphilis System to establish an adequate quality assurance program to ensure the performance of the device under specific locations and conditions of use.

The controls should be run under the following circumstances:

- With each new operator prior to performing tests on patient samples
- 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)
- 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.

8. INTERPRETATION OF RESULTS

8.1 HIV Results Interpretation:

- A nonreactive test result means that HIV-1 and HIV-2 antibodies were not detected in the specimen. The test result is interpreted as NEGATIVE for HIV-1 and HIV-2 antibodies. However, this does not exclude possible infection with HIV. Follow CDC guidelines to inform the test subject of the test result and its interpretation.

- A reactive test result means that HIV-1 and/or HIV-2 antibodies have been detected in the specimen. The test result is interpreted as Preliminary POSITIVE for HIV-1 and/or HIV-2 antibodies. Follow CDC guidelines to inform the test subject of the Test Result and its interpretation.

8.2 Syphilis Results Interpretation:

- A nonreactive syphilis result on the DPP HIV-Syphilis System does not exclude incubating or early primary syphilis.

- Test results are intended to aid in diagnosis only. As with all serological tests for syphilis, results should always be interpreted in conjunction with additional treponemal or nontreponemal serologic test results (as appropriate), the patient's clinical symptoms, medical history, and other clinical and/or laboratory findings. Diagnostic considerations should be based on treponemal and nontreponemal testing according to the CDC guidelines.

- Reactive test result for treponemal antibodies may indicate recent, past, or successfully treated syphilis. A reactive treponemal antibody test result on the DPP HIV-Syphilis System is not diagnostic of syphilis without additional nontreponemal serologic testing and a full clinical evaluation.

- A diagnosis of syphilis must be made in the context of treponemal and non-treponemal test results and in conjunction with clinical findings.

- This test is not intended for use as a confirmatory test in the reverse sequence syphilis screening algorithm, nor should it be used as the 2nd tier assay in the traditional sequence syphilis screening algorithm.

9. WARNINGS AND PRECAUTIONS

- For *in vitro* diagnostic use.
- Optimal performance of this test requires appropriate specimen collection and handling (refer to the Specimen Collection and Preparation for Analysis section of this package insert).

- The results of DPP HIV-Syphilis test are read and interpreted only by DPP Micro Reader with dedicated software. Results should not be read manually.
- Handle the samples and materials contacting samples, and kit controls as if capable of transmitting infection.
- Reading test results using the DPP Micro Reader earlier than 10 minutes or later than 25 minutes after the addition of DPP Running Buffer to BUFFER Well 2 may yield erroneous results.
- Do not open the sealed foil pouch until just prior to use.
- Do not use kit contents beyond labeled expiration date.
- Ensure finger is completely dry before performing fingerstick
- Do not eat, drink or smoke in the area where samples and kit reagents are handled.
- Avoid any contact between hands, eyes or mouth during sample collection and testing.
- Wear protective clothing such as laboratory coats, disposable gloves and eye protection when handling patient samples.
- Clean and disinfect spills of specimens by including the use of a tuberculocidal disinfectant such as (b) (4) sodium hypochlorite or other suitable disinfectant.
- Decontaminate and dispose of all potentially infectious materials in accordance with local, state, and federal regulations.
- To reduce the risk of invalid results, carefully read the entire package insert prior to performing this assay.
- Use only supplied or specified required consumables to ensure optimal test performance.

10. PROCEDUAL LIMITATIONS

- The DPP HIV-Syphilis System must ONLY be used with capillary (fingerstick) or potassium-EDTA venous whole blood or plasma.
- The DPP HIV-Syphilis System is intended to be used as the first-tier assay in the reverse sequence syphilis screening algorithm to aid in the detection of infection with *T. pallidum* (refer to the CDC 2015 STD Treatment Guidelines at (https://www.cdc.gov/std/tg2015/default.htm).
- A diagnosis of syphilis must be made in the context of treponemal and non-treponemal test results and in conjunction with clinical findings.
- This test is not intended for use as a confirmatory test in the reverse sequence syphilis screening algorithm, nor should it be used as the 2nd tier assay in the traditional sequence syphilis screening algorithm.
- An HIV REACTIVE result using the DPP HIV-Syphilis System suggests the presence of antibodies to HIV-1 and/or HIV-2 in the sample and the REACTIVE test result is interpreted as Preliminary Positive for HIV-1 and/or HIV-2 antibodies.

- A person who has antibodies to HIV-1 or HIV-2 is presumed to be infected with the virus, except that 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.
- A Syphilis REACTIVE result must be followed up with a non-treponemal test for syphilis, such as RPR, along with clinical evaluation, for diagnosis of syphilis.
- An individual infected with *Treponema pallidum* who is receiving antibacterial therapy may produce false negative results.
- REACTIVE test results are confirmed by additional testing.
- This test has not been evaluated for newborn screening, cord blood specimens, or individuals less than 13 years of age.
- A NONREACTIVE result does not preclude the possibility of exposure to HIV or *Treponema pallidum* bacteria or infection with HIV or *T. pallidum*. An antibody response to a recent exposure may take several months to reach detectable levels.
- Specimens from individuals with Systemic Lupus Erythematosus, anti-Double Stranded DNA Antibodies and Cytomegalovirus IgM antibodies may give false positive test results for syphilis.

11. CONTRAINDICATIONS

There are no known contraindications for this test.

12. ALTERNATIVE PRACTICES AND PROCEDURES

Detection of antibodies against HIV can be done in a variety of ways, including enzyme or chemiluminescent immunoassays, Western blot, and immunochromatographic assays which may be either lateral or transverse flow.

Treponemal antibodies to *T. pallidum* are typically identified via a variety of commercially available, FDA cleared serological methods, including the fluorescent treponemal antibody absorption (FTA-ABS) test, the *Treponema pallidum* particle agglutination (TP-PA) test, enzyme immunoassay (EIA) tests, and the Western blot test.

13. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects of the DPP HIV-Syphilis System relate to the risk of false positive and false negative results. While the performance studies indicate that this risk is likely to be very small, the potential for inaccurate results exist. The risk of incorrect results is minimized by following the procedures and instructions outlined in the Package Insert.

14. MARKETING HISTORY

This device has not been marketed previously.

15. SUMMARY OF PRECLINICAL STUDIES

15.1 Analytical Sensitivity (Assay Cutoff)

The DPP HIV-Syphilis System was developed as a qualitative assay with a target performance of high agreement with patient infection status for HIV and Syphilis determined as follows:

- HIV:
- Western Blot HIV testing algorithm, consisting of an HIV-1 EIA screen followed by confirmation via HIV-1 Western Blot and Nucleic Acid Testing (if Western Blot negative or indeterminate).
- 4th Generation HIV testing algorithm, consisting of an HIV 1/2 Antigen/Antibody assay with confirmation via an HIV-1/HIV-2 Differentiation Assay and Nucleic Acid Testing (if differentiation assay negative or indeterminate).

- Syphilis:
- Reverse Algorithm for syphilis, consisting of a treponemal antibody screen by an FDA cleared EIA assay, followed by Rapid Plasma Reagin (RPR) test and Treponema pallidum Particle Agglutination assay (TP-PA), if RPR negative.

The assay cutoffs for HIV and Syphilis were determined by ROC analysis of (b) (4) HIV positive specimens, (b) (4) HIV negative specimens, (b) (4) syphilis positive specimens, and (b) (4) syphilis negative specimens collected during clinical studies with patient infected status determined as per the algorithms described above. Results are read using the DPP Micro Reader which takes an internal measurement (i.e., not displayed to the end-user) of the signal intensity of each of the test lines and reports the results as REACTIVE or NONREACTIVE based on a preset cutoff. The cutoff values of each test line were determined to maximize sensitivity while maintaining specificity. Cutoff selection for HIV was further refined by testing (b) (4) HIV-1 seroconversion panels. The analytically selected cutoff for each test line was validated in a prospective clinical study in the intended use population.

15.2 Analytical Specificity

Cross-reactivity with Unrelated Medical Conditions

To evaluate the specificity of the DPP HIV-Syphilis System, serum samples from individuals diagnosed with various medical conditions unrelated to HIV or syphilis were tested for potential cross-reactivity. Specimens from at least 10 individuals per category were tested. Cross-reactivity was observed upon initial testing of samples containing CMV-IgM, DS-DNA and sera from SLE patients. To obtain a better understanding about the extent of the cross-reactivity, additional samples were tested for those categories. The results from the study are shown in Table 1.

Table 1: Performance of the DPP HIV-Syphilis System with Specimens Representing Various Unrelated Medical Conditions

Unrelated Medical Condition	Number	# Reactive by DPP (HIV)	# Reactive by DPP (Treponemal)
Cirrhosis	10	0	0
Cytomegalovirus (CMV) IgM	70	0	7[1]
Dialysis	10	0	0
Double Stranded DNA (dsDNA) Ab	72	0	8[2]
Epstein–Barr Virus (EBV) IgG	10	0	0
Hepatitis A Virus (HAV) IgM	10	0	0
Hepatitis B Virus (HBV) Ag	10	0	0
Hepatitis C Virus (HCV) Ab	10	0	0
HIV Ab	10	10	0
Herpes Simplex Virus (HSV)-1 IgG	10	0	0
Herpes Simplex Virus (HSV)-2 IgG	10	0	0
Human T-Lymphotropic Virus (HTLV) I/II	10	0	0
Syphilis	10	0	10
Lipemic	10	0	0
Lyme	10	0	0
Influenza Vaccine	10	0	0
Pregnant Females	12	0	0
Multiparous Females	10	0	0
Rheumatoid Factor	13	0	0
Varicella Zoster Virus (VZV) IgG	11	0	0
Tuberculosis	15	0	0
Drug Users (IVDU)	13	0	0
Leptospirosis	11	0	0
Systemic Lupus Erythematosus (SLE)	44	0	1[3]
Scleroderma	10	0	0
HAMA	10	0	0
Cardiolipin IgG	7	0	0
Cardiolipin IgM	8	0	0
Hypergammaglobulinemia IgA	9	0	0
Hypergammaglobulinemia IgE	10	0	0
Hypergammaglobulinemia IgG	10	0	0
Hypergammaglobulinemia IgM	10	0	0
Antiphospholipid Syndrome	3	0	0
Chlamydia	10	0	0
Gonorrhea	10	0	0
Total	508	10	26

[1]A total 70 CMV IgM specimens were tested on the DPP HIV-Syphilis System, of which 7 samples yielded reactive results on the Syphilis test line for an estimated cross-reactivity rate of 10.0% (7/70).

[2]A total of 72 dsDNA specimens were tested on the DPP HIV-Syphilis System, of which 8 yielded reactive results on the Syphilis test line for an estimated cross-reactivity rate of 11.1% (8/72).

[3]A total of 44 SLE specimens were tested on the DPP HIV-Syphilis System, of which 1 yielded reactive result on the Syphilis test line for an estimated cross-reactivity rate of 2.3% (1/44).

Effect of Interfering Substances on Analytical Sensitivity and Specificity

The effect of the following potentially interfering substances on assay performance was tested using 100 specimens representing potentially interfering substances. Interferences were tested up to the listed concentrations and no impact on results was observed.

Table 2: Interfering Substances – HIV Test Line, Reported as Number Correct/ Expected Results

Interfering Substance	Concentration Tested
Hemoglobin Samples	0.98 – 500 mg/dL
Triglyceride/Triolein	5.86 – 3,000 mg/dL
Bilirubin Mixed Isomer	0.04 – 20 mg/dL
Total Protein (HAS)	6.0 – 11.0 g/dL
E. coli	98 – 50,000 CFU/mL
EDTA	1.56 – 800 mg/dL
Sodium Citrate	1.95 – 1,000 mg/dL
Lithium Heparin	15.63 - 8,000 mg/dL
Sodium Heparin	15.63 – 8,000 mg/dL
Candida albicans	44 – 22,500 cells/mL

15.3 Specimen Stability Study

To evaluate specimen stability, specimens stored at the following conditions were tested with the DPP HIV-Syphilis System.

- Whole blood stored refrigerated (2-8°C) for (b) (4) days. Specimens were tested daily from Day 3 (b) (4) .
- Whole blood stored at room temperature (15-30°C) for (b) (4) days. Specimens were tested daily.
- Plasma stored frozen for prolonged period of time subjected to (b) (4) . Specimens were tested after the (b) (4) .

Results indicate that there was no impact on the test performance under the following conditions:

- Whole blood stored for (b) (4) days at 2-8°C.
- Whole blood stores for one to three days at (b) (4) °C.
- Plasma samples stored for (b) (4) days at 2-8°C.
- Plasma stored for one to three days at (b) (4) °C.
- Plasma stored at ≤ -20°C for (b) (4) days that had undergone (b) (4) .

15.4 Specimen Matrix Equivalency

Sixty-two matched serum and plasma samples were tested to determine specimen matrix equivalency. Thirty-one samples were tested unspiked and thirty-one samples were tested spiked with low levels of HIV-1 positive specimen, HIV-2 positive specimen or syphilis positive specimen. Results indicated that serum and plasma specimens were found to be in 100% agreement.

15.5. End Point Stability

To evaluate if a delay in the assay read time impacts the stability of the test results, HIV/Syphilis weakly reactive, HIV/Syphilis reactive and HIV/Syphilis negative samples were run on the DPP HIV-Syphilis System and the results were read and recorded at (b) (4), 10, 15, 25, (b) (4) minutes from the addition of the Running Buffer. Results indicate that the test results for HIV and Syphilis are stable for (b) (4) minutes from the addition of the Running Buffer.

15.6. The Effect of Under/Over Volume of the Sample and Running Buffer on Test Performance

The effect of adding under/over volume of the sample and running buffer on performance of the DPP HIV-Syphilis System was evaluated. HIV/Syphilis weakly reactive, HIV/Syphilis reactive and HIV/Syphilis negative whole blood samples were run on the DPP HIV-Syphilis System and the results were read. The addition of insufficient volume ((b) (4)) of sample and running buffer ((b) (4)) yielded the expected Invalid test result. The addition of excess volume of sample and running buffer had no impact on the test results (negative samples were non-reactive and positive samples were reactive).

15.7. Shipping, Environmental and Mechanical Stress Studies

To evaluate the impact of environmental and mechanical stress on the test performance, (b) (4) lots of the DPP HIV-Syphilis System were subjected to the following mechanical and environmental stress parameters:

- Temperature/humidity cycling – testing was between (b) (4) °C with uncontrolled humidity
- High altitude -- (b) (4) feet for (b) (4)
- Free Fall Drop -- dropped from a (b) (4) height a total of (b) (4) times
- Loose Cargo Vibrations – stressed with (b) (4) displacement bounces.

Visual examination of the components that had undergone stress testing indicated that all components appeared intact and uncompromised. Functional testing was also performed. The results indicated that

environmental and mechanical stress had very little impact on the packaging and function of the DPP HIV-syphilis System.

15.8. Stability Studies

Real time testing data using three validation lots of the DPP HIV-Syphilis System stored at the recommended storage temperature of 2-8° C and 25°C; and for three lots of the Sample Buffer and Running Buffer stored at the recommended storage temperature of 25°C were submitted up to the (b) (4)-month time point. All testing was performed using negative sample, HIV-1 low positive sample, HIV-2 low positive sample, Syphilis low positive sample and buffer only control. All samples yielded the expected results. Stability/expiry dating for the DPP HIV-Syphilis System will be for 24 months when stored at 2-25°C

15.9. HIV Analytical Performance

15.9.1. HIV-1/HIV-2 End Point Dilution Study

The performance of the DPP HIV-syphilis System to detect end-point dilutions of HIV-1 and HIV-2 antibodies were evaluated by testing serial dilutions of (b) (4) confirmed HIV-1 positive clinical specimens and (b) (4) confirmed HIV-2 positive clinical specimens. Results indicated that the performance of the DPP HIV-syphilis System was equivalent to or better than the FDA approved comparator assay.

15.9.2. HIV-1 Antibody Mixed Titer Panel Testing

The analytical performance of the DPP HIV-Syphilis Assay System was evaluated using one mixed titer panel. The panel members ranged from negative to highly reactive plasma specimens. The results indicated that the DPP HIV-Syphilis System detected (b) (4) panel members as reactive and the FDA approved comparator assay detected (b) (4) panel members as reactive. The results demonstrated that the DPP HIV-Syphilis System was equivalent to the FDA approved comparator assay in detecting antibodies to HIV-1.

15.9.3. HIV-1 Low Titer Panel Testing

The analytical performance of the DPP HIV-Syphilis System was evaluated using one HIV-1 low titer panel. The panel members consisted of (b) (4) well characterized HIV-1 low titer plasma specimens. The results indicated that the DPP HIV-Syphilis Assay System detected (b) (4) panel members and the FDA approved comparator assay detected (b) (4) low titer panel members. The results demonstrated that the DPP HIV-Syphilis System was equivalent to the FDA approved comparator assay in detecting antibodies to HIV-1 in low titer panels.

15.9.4. HIV-1 Seroconversion Panels (Comparison to EIA)

Twenty-five commercially available HIV-1 seroconversion panels were tested. Each panel consisted of sequential collections from a single seroconverted individual. Table 3 presents the days first reactive bleed. Data are presented for two FDA licensed EIA tests and the DPP HIV-Syphilis System.

Table 3: Testing HIV-1 Seroconversion Panels Using the Chembio DPP HIV Syphilis System

Panel	Day of first reactive results			Days detected earlier by DPP HIV- Syphilis System	
	DPP HIV-Syphilis System	EIA1	EIA2	EIA1	EIA2
PRB917	65	60	72	-5	7
PRB924	35	33	35	-2	0
PRB927	33	28	40	-5	7
PRB929	28	25	28	-3	0
PRB930	10	7	10	-3	0
PRB939	103	103	103	0	0
PRB944	14	14	ND	0	2
PRB945	20	13	ND	-7	-
PRB947	20	9	20	-11	0
PRB955	14	12	14	-2	0
PRB968	33	28	28	-5	-5
PRB969	72	70	70	-2	-2
9014	10	10	24	0	14
9031	153	146	157	-7	4
9032	49	24	29	-25	-20
9075	30	30	30	0	0
9077	52	57	52	5	0
12007	126	119	126	-7	0
9079	57	47	47	-10	-10
HIV-002	33	31	NT	-2	N/A
HIV-003	47	47	NT	0	N/A
HIV-007	27	14	NT	-7	N/A

ND = Not Detected, NT = Not Tested, N/A = Not Applicable

Sixteen panels tested reactive earlier in the EIA 1 test as compared to the DPP HIV-Syphilis system, five panels tested reactive on the same bleed in both tests (EIA 1 and DPP HIV-Syphilis system) and only one panel tested reactive 5 days earlier using DPP HIV-Syphilis system compared to EIA 1 test. Five panels test results are missing using EIA 2. Six panels tested earlier using DPP HIV-Syphilis test compared to EIA 2, eight panels tested reactive at the same time interval in

both tests (EIA 2 and DPP HIV-Syphilis system) and six panels tested reactive earlier in the EIA 2 test as compared to the DPP HIV-Syphilis system.

15.9.5. Reactivity with HIV-1 Subtypes and HIV-1 Group O

A total of 213 specimens (serum/plasma) from different geographical regions were tested to assess the ability of the DPP HIV-Syphilis System to detect HIV-1 antibodies directed to different HIV-1 group M subtypes and HIV-1 Group O. All 213 specimens were Reactive with the DPP HIV-Syphilis System for an overall sensitivity of 100% (95% CI = 98.3% to 100%). The results are presented in Table 4.

Table 4: Reactivity with HIV-1 Subtypes and HIV-1 Group O Specimens

HIV Subtype	Number of Specimens	DPP HIV-Syphilis System Reactive
A	30	30
AE	15	15
AG	30	30
B	5	5
B/D	1	1
C	39	39
D	19	19
F	9	9
G	20	20
H	7	7
J	2	2
K	3	3
CRF01/CRF15	1	1
CRF01_AE	2	2
CRF02_AG	3	3
CRF03_AB	2	2
G/CRF02	1	1
H/A1	1	1
K/CRF09	1	1
URF_01A1G	1	1
URF_A1C	2	2
URF_A1CD	2	2
URF_A1D	8	8
URF_CD	1	1
Recomb. Of F1, K	2	2
Recomb. Of G, K	1	1
Recomb. Of K, A1	1	1
HIV-1 Group O	4	4
TOTAL	213	213

15.9.6. Viral Co-Infection Panel Detection

The performance of the DPP HIV-Syphilis Assay to detect antibodies to HIV in well characterized viral co-infection panels was evaluated. (b) (4) viral co-infection panels were tested. (b) (4) plasma specimens were from HIV-1/2 and HCV co-infected individuals and (b) (4) plasma specimen was from HIV-1/2 and HBV co-infected individual. Of the (b) (4) specimens tested with the DPP HIV-Syphilis assay, (b) (4) specimens were reactive for HIV and (b) (4) specimens were non-reactive. The (b) (4) non-reactive specimens were confirmed negative on an FDA approved supplemental assay. The results demonstrate that the DPP HIV-Syphilis Assay System was able to detect HIV antibodies in HIV and HCV/HBV co-infected samples.

16. REPRODUCIBILITY

16.1. Reproducibility in Venous Whole Blood

The reproducibility of the DPP HIV-Syphilis System in whole blood matrix was evaluated in a study conducted at three external testing sites, with two operators at each site, testing a 6-member sample panel twice per day over 5 days using one lot of test cassettes. Each sample was tested in duplicate. The test samples were contrived in whole blood matrix corresponding to low reactive ((b) (4)) and near cutoff ((b) (4)) reactive levels of HIV and treponemal antibodies. The antibody concentrations were targeted based on the reflectance signal value from the Micro Reader. The characteristics of the reproducibility test panel are shown in Table 5.

Table 5: Reproducibility Test Panel (Whole Blood)

Panel Member		HIV		Syphilis	
	Target Concentration	**Target Micro Reader Signal**	**Expected Result**	**Target Micro Reader Signal**	**Expected Result**
1	No analyte (whole blood matrix)	(b) (4)	Non-Reactive	(b) (4)	Non-Reactive
2	Low Reactive (b) (4) (HIV-1)		Reactive		Non-Reactive
3	Low Reactive (b) (4) (HIV-2)		Reactive		Non-Reactive
4	Low Reactive (b) (4) Syphilis		Non-Reactive		Reactive
5	Near Cutoff (b) (4) (HIV-1)		Reactive		Non-Reactive
6	Near Cutoff (b) (4) Syphilis		Non-Reactive		Reactive

Testing was performed according to the Product Insert of the DPP HIV-Syphilis Assay. Results were read at 10 minutes using DPP Micro Reader. The results from the reproducibility study are shown in Tables 6-8.

Table 6: Reproducibility Study Results (Whole Blood), All Sites, All Operators, All Days

Sample	HIV Test Line	Syphilis Test Line
	% Agreement with Expected Result	% Agreement with Expected Result
	(No. Reactive/No. Tested)	(No. Reactive/No. Tested)
Low Reactive HIV-1	100% (120/120)	97.5% (3/120)
Low Reactive HIV-2	100% (120/120)	100% (0/120)
Low Reactive Syphilis	100% (0/120)	100% (120/120)
Nonreactive	100% (0/120)	99.2% (1/120)
Near Cutoff Reactive HIV-1	93.3% (112/120)	99.2% (1/120)
Near Cutoff Reactive Syphilis	100% (0/120)	95.8% (115/120)

Table 7: Reproducibility Study Results (Whole Blood) by Sites

Sample	HIV Test Line (No. Reactive / No. Tested)			Syphilis Test Line (No. Reactive / No. Tested)		
	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Low Reactive HIV-1	40/40	40/40	40/40	0/40	0/40	3/40
Low Reactive HIV-2	40/40	40/40	40/40	0/40	0/40	0/40
Low Reactive Syphilis	0/40	0/40	0/40	40/40	40/40	40/40
Nonreactive	40/40	40/40	40/40	39/40	40/40	40/40
Near Cutoff Reactive HIV-1	37/40	40/40	35/40	1/40	0/40	0/40
Near Cutoff Reactive Syphilis	0/40	0/40	0/40	38/40	40/40	37/40

Table 8: Reproducibility Study Results (Whole Blood), by Sites and by Operators

Sample	HIV Test Line Results No. Reactive/ No Tested (% Agreement with Expected Results)						Syphilis Test Line Results No. Reactive/ No Tested (% Agreement with Expected Results)					
	Site: (b) (4)		Site: (b) (4)		Site: (b) (4)		Site: (b) (4)		Site: (b) (4)		Site: (b) (4)	
	Op 1	Op 2	Op 1	Op 2	Op 1	Op 2	Op 1	Op 2	Op 1	Op 2	Op 1	Op 2
Low Reactive	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	1/20 (95%)	2/20 (90%)
Low Reactive HIV-2	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)
Low Reactive Syphilis	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)
Nonreactive	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	1/20 (95%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)
Near Cutoff Reactive (HIV-1	18/20 (90%)	19/20 (95%)	20/20 (100%)	20/20 (100%)	16/20 (80%)	19/20 (95%)	1/20 (95%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)
Near Cutoff Reactive Syphilis	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	0/20 (100%)	18/20 (90%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	17/20 (85%)

16.2. Reproducibility in Plasma

The reproducibility of the DPP HIV-Syphilis System was also evaluated when used with plasma samples. This study was conducted at three laboratory sites using a panel of eight blinded plasma samples, as described in Table 9.

Table 9: Reproducibility Test Panel (Plasma)

		HIV		Syphilis	
	Target Concentration	**Target Micro Reader Signal**	**Expected Result**	**Target Micro Reader Signal**	**Expected Result**
1	No analyte (whole blood matrix)	(b) (4)	Non-Reactive	(b) (4)	Non-Reactive
2	Low Reactive (b) (4) (HIV-1)		Reactive		Non-Reactive
3	Low Reactive (b) (4) (HIV-2)		Reactive		Non-Reactive
4	Low Reactive (b) (4) (Syphilis)		Non-Reactive		Reactive
5	Low Reactive (b) (4) (HIV-1 and Syphilis)		Reactive		Reactive
6	High Reactive (b) (4) (HIV-1)		Reactive		Non-Reactive
7	High Reactive (b) (4) (HIV-2)		Reactive		Non-Reactive
8	High Reactive (b) (4) (Syphilis)		Non-Reactive		Reactive

Each panel was run on 3 lots of the DPP HIV-Syphilis System on 3 separate days by 3 separate operators at each site. Results were read at 10 minutes, using the DPP Micro Reader. The results of the reproducibility study in plasma are presented in Tables 10 and 11.

Table 10: Reproducibility Study Results (Plasma), All Sites, All Operators, All Days

Sample	HIV Test Line % Agreement with Expected Result (No. Reactive/No. Tested)	Treponemal Test Line % Agreement with Expected Result (No. Reactive/No. Tested)
HIV-1 Low Reactive	100% (81/81)	100% (0/81)
HIV-2 Low Reactive	100% (81/81)	100% (0/81)
Treponemal Antibody Low Reactive	100% (0/81)	100% (81/81)
HIV-1 and Treponemal Antibody Low Reactive	100% (81/81)	98.8% (80/81)
HIV-1 High Reactive	100% (81/81)	100% (0/81)
HIV-2 High Reactive	100% (81/81)	100% (0/81)
Treponemal Antibody High Reactive	100% (0/81)	98.8% (80/81)
Nonreactive	100% (0/81)	98.8% (1/81)

Table 11: Reproducibility Study Results (Plasma) by Sites

Sample	HIV Test Line (No. Expected / No. Tested)			Treponemal Test Line (No. Expected / No. Tested)		
	Site 1	Site 2	Site 3	Site 1	Site 2	Site 3
HIV-1 Low Reactive	27/27	27/27	27/27	27/27	27/27	27/27
HIV-2 Low Reactive	27/27	27/27	27/27	27/27	27/27	27/27
Treponemal Antibody Low Reactive	27/27	27/27	27/27	27/27	27/27	27/27
HIV-1 and Treponemal Antibody Low Reactive	27/27	27/27	27/27	26/27	27/27	27/27
HIV-1 High Reactive	27/27	27/27	27/27	27/27	27/27	27/27
HIV-2 High Reactive	27/27	27/27	27/27	27/27	27/27	27/27
Treponemal Antibody High Reactive	27/27	27/27	27/27	27/27	26/27	27/27
Nonreactive	27/27	27/27	27/27	27/27	26/27	27/27

17. SUMMARY OF CLINICAL STUDIES

17.1 HIV-1 Sensitivity

17.1.1 Capillary (Fingerstick) Whole Blood

The sensitivity of the DPP HIV-Syphilis System to detect HIV-1 infection in Fingerstick whole blood was evaluated using 619 samples from individuals known to be infected with HIV-1 using HIV 1/2 Ag/Ab EIA. A total of 468 were Known Positive for HIV-1 only and 151 were Known Positive for both HIV-1 and Syphilis. Six hundred fifteen (615) samples out of 619 tested HIV Reactive using the DPP HIV-Syphilis System. The four false non-reactive results were from individuals on Highly Active Antiretroviral Therapy (HAART).

In addition, samples from 91 individuals Known Positive for Syphilis only, 728 individuals at a High Risk for HIV and Syphilis infection, and 558 individuals at Low Risk for HIV and Syphilis infection were tested. Samples from these groups were tested for HIV by an HIV 1/2 Ag/Ab EIA and if reactive were confirmed using an HIV-1/HIV-2 Differentiation Assay. Of the 91 Known Positive Syphilis only individuals, six were confirmed HIV positive. Of the 728 high-risk individuals, 13 were confirmed HIV positive, and of the 558 low-risk individuals, only 1 was confirmed HIV positive. All 20 (6+13+1) of these samples were HIV reactive on the DPP HIV-Syphilis System (Table 12).

Table 12: Detection of Antibody to HIV-1 in Capillary Whole Blood (Fingerstick) Specimens from Individuals Known to be Infected with HIV-1 and at High Risk for Infection with HIV-1

Infection Status	DPP HIV-Syphilis System - HIV Result		Total
	Reactive	Nonreactive	
Positive	635	4[1]	639
Negative	5	1352	1357
Total	640	1356	1996

[1]All 4 false non-reactive results were from individuals on HAART

Summary: The sensitivity of the DPP HIV-Syphilis System was evaluated using 639 specimens (619 known HIV- 1 positives, 19 true positives identified from the high-risk population and one true positive identified from the low risk population) (see Table 16 below). When fingerstick whole blood was tested, 635 specimens tested Reactive using the DPP HIV-Syphilis System (615 known positive, 19 high risk and 1 low risk) and false Nonreactive for four confirmed positive specimens from known positive individuals. The calculated HIV sensitivity of 635/639 = 99.4% (95% Confidence Interval = 98.4% - 99.8%).

17.1.2. Venous Whole Blood

The sensitivity of the DPP HIV-Syphilis System to detect HIV-1 infection in venous whole blood was evaluated using 618 samples from individuals known to be infected with HIV-1 using HIV 1/2 Ag/Ab EIA, 151 of which were Known Positive for both HIV- 1 and Syphilis, and 467 were Known Positive for HIV-1 only. Six hundred fifteen (615) samples out of 618 tested HIV Reactive using the DPP HIV-Syphilis System. Of the 3 false nonreactive individuals 2 were on HAART.

In addition, samples from 91 individuals Known Positive for Syphilis only, 729 individuals at a High Risk for HIV and Syphilis infection, and 559 individuals Low Risk for HIV and Syphilis infection were tested. Samples from these groups were tested for HIV by an HIV 1/2 Ag/Ab EIA and if reactive were confirmed using an HIV-1/HIV-2 Differentiation Assay. Of the 91 Known Positive Syphilis only individuals, 6 were confirmed HIV positive, of the 728 High Risk individuals, 13 were confirmed HIV positive, and of the 559 Low Risk individuals, 1 was confirmed HIV positive. All 20 (6+13+1) of these samples were HIV reactive on the DPP HIV-Syphilis System (Table 13).

Table 13: Detection of Antibody to HIV-1 in Venous Whole Blood Specimens from Individuals Known to be Infected with HIV-1 and at High Risk for Infection with HIV-1

Infection Status	DPP HIV-Syphilis System - HIV Result		Total
	Reactive	Non-reactive	
Positive	635	3[1]	638
Negative	7	1352	1359
Total	642	1355	1997

[1]Of 3 false nonreactive individuals 2 were on HAART.

Summary: The sensitivity of the DPP HIV-Syphilis System was evaluated using 638 specimens (618 known HIV- 1 positives and 19 true positives identified from the high-risk population and 1 true positive identified from the low risk population) (see Table 10). Of these, 635 specimens tested Reactive using the DPP HIV-Syphilis System (615 known positive, 19 high risk and 1 low risk). In these studies, the DPP HIV-Syphilis System gave false Nonreactive results for three confirmed positive specimens from known positive individuals. The calculated HIV sensitivity of the DPP HIV-Syphilis System for Venous whole blood was 635/638 = 99.5% (95% Confidence Interval = 98.6% - 99.8%).

17.1.3. Plasma

The sensitivity of the DPP HIV-Syphilis System to detect HIV- 1 infection in plasma was evaluated using 398 samples from individuals known to be infected with HIV-1 using HIV 1/2 Ag/Ab EIA. 101 of these were Known Positive for both HIV-1 and Syphilis, and 297 were Known Positive for HIV-1 only. Three hundred

ninety-five (395) samples out of 398 tested HIV Reactive using the DPP HIV-Syphilis System. All 3 false nonreactive results were from individuals on HAART.

In addition, samples from 75 individuals Known Positive for Syphilis only, from 422 individuals at a High Risk for HIV and Syphilis infection, and from 419 individuals at a Low Risk for HIV and Syphilis infection were tested. Samples from these groups were tested for HIV by an HIV 1/2 Ag/Ab EIA and if reactive were confirmed using an HIV-1/HIV-2 Differentiation Assay. Of the 75 Known Positive Syphilis only individuals, 5 were confirmed HIV positive; of the 422 High Risk individuals, 4 were confirmed HIV positive; and of the 419 Low Risk individuals, 1 was confirmed HIV positive. All 10 of these samples were HIV reactive on the DPP HIV- Syphilis System (Table 14).

Table 14: Detection of Antibody to HIV-1 in Plasma Specimens from Individuals Known to be Infected with HIV-1 and at High Risk for Infection with HIV-1

Infection Status	DPP HIV-Syphilis System HIV-1 Result		Total
	Reactive	Nonreactive	
Positive	405	3[1]	408
Negative	4	902	906
Total	409	905	1314

[1]All 3 false nonreactive results were from individuals on HAART.

Summary: The sensitivity of the DPP HIV-Syphilis System was evaluated using 408 specimens (398 known HIV- 1 positives and 9 true positives identified from the high-risk population and 1 true positive identified from the low risk population). Of these, 405 specimens tested Reactive using the DPP HIV-Syphilis System (395 known positive, 9 high risk and 1 low risk). There were false Nonreactive results for three confirmed positive specimens from known positive individuals. The calculated HIV sensitivity of the OPP HIV-Syphilis System for plasma was 405/408 = 99.3% (95% Confidence Interval = 97.9% - 99.7%).

17.2. HIV-2 Sensitivity

The sensitivity of the DPP HIV-Syphilis System to detect HIV-2 antibody was determined by testing 210 serum/plasma specimens that were positive for HIV-2 antibodies only. These specimens were obtained from repository sources. A total of 546 specimens from an area endemic for HIV-2 infection were also tested. All specimens reactive with the DPP HIV-Syphilis System were also reactive by FDA approved/licensed HIV 1/2 Assays (Table 15).

Table 15: Detection of Antibody to HIV-2 in Known HIV-2 Reactive Specimens and Endemic Samples

Study Population	Samples	DPP HIV-Syphilis System Reactive	True HIV-2 Positive Only[1]
Known HIV-2 Positive	210	210	210
Endemic samples	546	196[2]	0
Total	756	406	210

[1] Confirmation based on results using research HIV-2 Western Blot
[2] Of 196 reactive specimens, 91 were reactive on HIV-1 WB only, 105 were reactive on HIV-1 and HIV-2 WB.

Summary: The sensitivity of DPP HIV-Syphilis System for detection of antibodies to HIV-2 in these studies was calculated to be 210/210 = 100% with the 95% confidence interval extending from 98.3 to 100%.

17.3 Specificity

17.3.1 Capillary (Fingerstick) Whole Blood

The HIV specificity of the DPP HIV-Syphilis System was evaluated by testing fingerstick blood specimens from 91 Syphilis Known Positive only, 728 High Risk, and 558 individuals Low Risk for HIV and Syphilis infection at 7 clinical study sites. Specimens were tested with an HIV 1/2 Ag/Ab EIA and nonreactive results were determined Negative for HIV (Table 16).

Table 16: Performance of the DPP HIV-Syphilis System on Capillary Whole Blood (Fingerstick) Specimens from Individuals Presumed to be Negative for HIV-1 Infection

Study Population	Samples	True HIV Negative	DPP HIV-Syphilis System Nonreactive
Syphilis Known Positive	91	85	85
High Risk for HIV	728	715	711
Low Risk for HIV	558	557	556
Total	1377	1357	1352

Summary: Specimens from 6 Syphilis Known Positive, 13 high risk and 1 low risk individuals that were reactive on a licensed HIV- 1/2 Ag/Ab EIA were excluded from these calculations. The HIV specificity of DPP HIV-Syphilis System was calculated to be 1352/1357 = 99.6% with the 95% confidence of 99.1- 99.8%.

17.3.2 Venous Whole Blood

The HIV specificity of the DPP HIV-Syphilis System was evaluated by testing Venous Whole Blood specimens from 91 Syphilis Known Positive only, 729 High Risk, and 559 individuals Low Risk for HIV and Syphilis infection at 7 clinical study sites. Specimens were tested with an HIV 1/2 Ag/Ab EIA and nonreactive results were determined Negative for HIV (Table 17).

Table 17: Performance of the DPP HIV-Syphilis System on Venous Whole Blood Specimens from Individuals Presumed to be Negative for HIV-1 Infection

Study Population	Samples	True HIV Negative	DPP HIV-Syphilis System Nonreactive
Syphilis Known Positive	91	85	84
High Risk HIV	729	716	711
Low Risk for HIV	559	558	557
Total	1379	1359	1352

Summary: Specimens from 6 Syphilis Known Positive, 13 high risk and 2 low risk individuals were reactive on a licensed HIV-1/2 Ag/Ab EIA and were excluded from these calculations. Based on these studies, the HIV specificity of DDP HIV-Syphilis System was calculated to be 1352/1359 = 99.5% with the 95% confidence interval of 98.9 - 99.8

17.3.3 Plasma

The HIV specificity of the DPP HIV-Syphilis System was evaluated by testing plasma specimens from 91 Syphilis Known Positive only, 729 High Risk, and 559 individuals Low Risk for HIV and Syphilis infection at 7 clinical study sites. Specimens were tested with an HIV 1/2 Ag /Ab EIA and nonreactive results were determined Negative for HIV (Table 18).

Table 18: Performance of the DPP HIV-Syphilis System on Plasma Specimens from Individuals Presumed to be Negative for HIV-1 Infection

Study Population	Samples	True Negative	DPP HIV-Syphilis System Nonreactive
Syphilis Known Positive	75	70	70
High Risk for HIV	422	418	417
Low Risk for HIV	419	418	417
Total	916	906	902

Summary: Specimens from 5 Syphilis Known Positive, 4 high risk and 1 low risk individuals were reactive on a licensed HIV-1/2 Ag/Ab EIA and were excluded from these calculations. Based on these studies, the HIV specificity of DPP HIV-Syphilis System in plasma specimens was calculated to be 902/906 = 99.6% with the 95% confidence interval of 98.9 to 99.8%.

17.4 Clinical Performance for Syphilis

The clinical performance of the DPP HIV-Syphilis System for the detection of treponemal antibodies was evaluated in a prospective study with 1529 individuals representing the intended use population, including subjects referred for routine syphilis testing, pregnant women, those previously diagnosed with syphilis, and those known to be positive for HIV-1 at enrollment. The study sites included HIV/STD Testing Clinics/Outreach Centers, Primary Care Clinics, Obstetrics and Gynecology (OB/GYN) Centers and an Outpatient Addiction Treatment Center. From among the 1529 individuals, 1282 fingerstick (FS) whole blood samples were available for testing (629 female, 653 male, 16 – 87 years old), 1280 venous whole blood samples were available for testing (627 female, 653 male, 16 – 87 years old), and 1163 plasma samples were available for testing (638 female, 525 male, 16 – 91 years old). The demographics of the intended use population for each study cohort are presented in Table 19.

Table 19: Study Subjects Demographics for Syphilis Evaluation

Matrix	Cohort	#Subjects	# Female	# Male	Age Range (yrs)
Fingerstick	Routine Syphilis	704	200	504	16 - 87
	HIV Positive at Enrollment	171	22	149	18 - 75
	Pregnant Women	407	407	N/A	18 - 43
	Total	**1282**	**629**	**653**	**16 – 87**
Venous Blood	Routine Syphilis	704	200	504	16 – 87
	HIV Positive at Enrollment	171	22	149	18 - 75
	Pregnant Women	405	405	N/A	18 - 43
	Total	**1280**	**627**	**653**	**16 - 87**
Plasma	Routine Syphilis	688	226	462	16 - 91
	HIV Positive at Enrollment	68	5	63	23 - 75
	Pregnant Women	407	407	N/A	18 - 43
	Total	**1163**	**638**	**525**	**16 - 91**

The clinical performance for the DPP HIV-Syphilis assay in detecting treponemal antibodies was estimated by calculating positive percent agreement (PPA) and negative percent agreement (NPA) of the DPP HIV-Syphilis System test results with the Final Comparator result, which was based on a serologic comparator algorithm of treponemal and non-treponemal antibody tests for syphilis. Blood samples collected from each individual were subjected to testing by three FDA-cleared syphilis assays: a treponemal EIA, a non-treponemal assay (RPR) and a second treponemal assay (TPPA). The Final Comparator result was determined to be Positive when at least two tests generated reactive results. Similarly, a

Negative Final Comparator result was determined when at least two of the tests generated non-reactive results. Table 20 shows how the Final Comparator results were determined based on the outcome of the three tests for syphilis.

Table 20: Serologic Comparator Algorithm for Treponemal Antibodies

1st Treponemal Test (EIA)	Non-Treponemal (RPR)	2nd Treponemal Test (TPPA)	Final Comparator Result
Nonreactive	Nonreactive	Reactive	Negative
		Nonreactive	Negative
		Inconclusive	Negative
Nonreactive	Reactive	Reactive	Positive
		Nonreactive	Negative
		Inconclusive	Negative[1]
Reactive	Reactive	Reactive	Positive
		Nonreactive	Positive
		Inconclusive	Positive
Reactive	Nonreactive	Reactive	Positive
		Nonreactive	Negative
		Inconclusive	Positive[2]
Equivocal	Nonreactive	Reactive	Positive
		Nonreactive	Negative
		Inconclusive	Indeterminate
Equivocal	Reactive	Reactive	Positive
		Nonreactive	Negative
		Inconclusive	Indeterminate

[1]The final comparator result of Negative was assigned based on the nonreactive treponemal test. There were no subjects with this serological profile among the study population.

[2]The final comparator result of Positive was assigned based on the reactive treponemal test. There were 5 subjects with this serological profile among the prospective study population.

The clinical performance of the DPP HIV-Syphilis System for detection of treponemal antibodies from prospectively enrolled subjects is shown in Tables 21-23 as percent agreement with the Final Comparator Result in FS whole blood, venous whole blood and plasma, overall and also by cohort.

Table 21: Performance of the DPP HIV-Syphilis System for Treponemal Antibodies in Fingerstick Specimens (all prospective), by Study Cohort Percent Agreement with the Final Comparator Result

Cohort	Positive Percent Agreement (PPA)			Negative Percent Agreement (NPA)		
	%	Ratio	95% CI	%	Ratio	95% CI
Routine Syphilis	92.5%	49 / 53	82.1 - 97.0%	97.1%	632 / 651	95.5 - 98.1%
HIV Positive at Enrollment	96.6%	57 / 59	88.5 - 99.1%	95.5%	107 / 112	90.0 - 98.1%
Pregnant Women	100.0	2 / 2	N/A	93.1%	377 / 405	90.2 - 95.2%
Total	94.7%	108 / 114	89.0 - 97.6%	95.5%	1116 / 1168	94.2 - 96.6%

Table 22: Performance of the DPP HIV-Syphilis System for Treponemal Antibodies in Venous Whole Blood (all prospective), by Study Cohort Percent Agreement with the Final Comparator Result

Cohort	Positive Percent Agreement (PPA)			Negative Percent Agreement (NPA)		
	%	Ratio	95% CI	%	Ratio	95% CI
Routine Syphilis	96.2 %	51 / 53	87.2 - 99.0%	96.3 %	627 / 651	94.6 - 97.5%
HIV Positive at Enrollment	96.6 %	57 / 59	88.5 - 99.1%	95.5 %	107 / 112	90.0 - 98.1%
Pregnant Women	100%	2 / 2	N/A	90.8 %	366 / 403	87.6 - 93.3%
Total	96.5 %	110 / 114	91.3 - 98.6%	94.3 %	1100 / 1166	92.9 - 95.5%

Table 23: Performance of the DPP HIV-Syphilis System for Treponemal Antibodies in Plasma Samples (by cohort) Percent Agreement with the Final Comparator Result

Cohort	Positive Percent Agreement (PPA)			Negative Percent Agreement (NPA)		
	%	Ratio	95% CI	%	Ratio	95% CI
Routine Syphilis	94.9%	37 / 39[1]	83.1 - 98.6%	95.1%	617 / 649[2]	93.1 - 96.5%
HIV Positive at Enrollment	100.0 %	21 / 21	84.5 - 100.0%	97.9%	46 / 47	88.9 - 99.6%
Pregnant Women	100.0 %	2 / 2	N/A	91.6%	371 / 405	88.5 - 93.9%
Total	96.8%	60 / 62	89.0 - 99.1%	93.9%	1034 / 1101	92.3 - 95.2%

[1]Includes sample from 1 subject of Unknown HIV Status
[2]Includes samples from 106 subjects of Unknown HIV Status

Clinical Performance in Pregnant Women

The treponemal test line performance of the DPP HIV-Syphilis System in pregnant women was evaluated in prospectively collected fingerstick whole blood samples (n=407), venous whole blood (n=405) and plasma samples (n=407) that were established as positive or negative for syphilis antibodies via the serological comparator algorithm for syphilis where individuals were screened using both treponemal (EIA) and non-treponemal (RPR) antibody tests, and subsequently tested on a 2nd treponemal antibody test (TPPA) if the initial treponemal and non-treponemal tests disagreed (Table 24).

Table 24: Performance of the DPP HIV-Syphilis System for Treponemal Antibodies with Samples Prospectively Collected from Pregnant Women Percent Agreement with the Final Comparator Result

Trimester	Positive Percent Agreement (PPA) % (Ratio) (95% CI)			Negative Percent Agreement (PPA) % (Ratio) (95% CI)		
	Fingerstick	Venous Blood	Plasma	Fingerstick	Venous Blood	Plasma
1st	100 (1/1) (20.7 – 100)	100 (1/1) (20.7 – 100)	100 (1/1) (20.7 – 100)	92.1 (140/152) (86.7 – 95.4)	90.8 (138/152) (85.1 – 94.4)	92.1 (140/152) (86.7 – 95.4)
2nd	100 (1/1) (20.7 – 100)	100 (1/1) (20.7 – 100)	100 (1/1) (20.7 – 100)	96.5 (109/113) (91.3 – 98.6)	93.8 (106/113) (87.8 – 97.0)	91.2 (103/113) (84.5 – 95.1)
3rd	N/A (0/0)	N/A (0/0)	N/A (0/0)	91.4 (128/140) (85.6 – 95.0)	88.4 (122/138) (82.0 – 92.7)	91.4 (128/140) (85.6 – 95.0)

Additionally, treponemal test line performance in pregnant women was also evaluated using 34 retrospectively collected plasma samples purchased from a commercial vendor that were presumed positive for Syphilis infection when tested (Table 25). The retrospective samples included 12 samples that had been tested using an FDA cleared test for non-treponemal antibodies (RPR with titer) and 22 samples that had been tested using FDA cleared tests for treponemal antibodies (IgG) as well as non-treponemal antibodies (RPR with titer).

Table 25: Performance of the DPP HIV-Syphilis System for Treponemal Antibodies with Samples from Pregnant Women Presumed Positive for Syphilis (Retrospective)

Syphilis Stage	Treatment Status	Trimester	N	DPP HIV-Syphilis System Nonreactive	DPP HIV-Syphilis System Reactive
Primary	Treated	Unknown	0	0	N/A
	Untreated	Unknown	3	0	100%
Secondary	Treated	Unknown	0	0	N/A
	Untreated	Unknown	1	0	100%
Early Latent	Treated	Unknown	0	0	N/A
	Untreated	Unknown	5	0	100%
Latent	Treated	Unknown	0	0	N/A
	Untreated	Unknown	3	0	100%
Unknown	Unknown	1st	8	0	100%
		2nd	6	0	100%
		3rd	8	0	100%
Total			34	0	0

Reactivity in Specimens from Individuals with Medically Diagnosed Syphilis

To assess the performance of the DPP HIV-Syphilis System in detecting treponemal antibodies using various medically staged syphilis specimens, 163 samples representing various clinical stages of syphilis diagnosis (primary, secondary, and latent) and treatment status were tested. The DPP HIV-Syphilis System was reactive in all 163 patients tested, as shown in Table 26.

Table 26: DPP HIV-Syphilis System Results for Treponemal Antibodies in Medically Staged Syphilis Samples

Syphilis Stage	Treatment Status	N	DPP HIV-Syphilis System Nonreactive	DPP HIV-Syphilis System Reactive
Primary	Treated	18	0	100%
	Untreated	10	0	100%
Secondary	Treated	33	0	100%
	Untreated	30	0	100%
Latent	Treated	42	0	100%
	Untreated	30	0	100%
Total		163	0	100%

18. INSPECTIONS

18.1 Manufacturing Facilities Review/Inspection

The manufacturing facility was waived from inspection**.**

Location	Activity	Inspection/Waiver	Most Recent Inspection
Chembio Diagnostic Systems Inc. 3661 Horseblock Road Medford, NY 11763 FEI:2431980	Device Manufacture, Release Testing	Waived	March 2018 Surveillance NYK-DO VAI August 2016 Surveillance NYK-DO VAI

VAI: Voluntary action indicated

18.2 Bioresearch Monitoring (BIMO) inspections

Bioresearch Monitoring (BIMO) inspections were conducted at two domestic clinical investigator sites that participated in the conduct of study Protocol CP-HIV-SYPH03. The inspections did not reveal substantive problems impacting the data submitted in support of this Pre-Market Application (PMA).

19. CONCLUSIONS DRAWN FROM THE STUDIES

19.1 Effectiveness Conclusions

The clinical study results, in combination with the non-clinical performance evaluations strongly support the effectiveness of the DPP HIV-Syphilis System for the medical intended use.

The HIV sensitivity and specificity of the DPP HIV-Syphilis System for all specimen types (fingerstick whole blood, venous whole blood and plasma) are greater than or equal to 99% with the lower boundary of the 95% confidence interval greater than or equal to 98% for all sample types.

The *T. pallidum* sensitivity and specificity of the DPP HIV-Syphilis System for all specimen types (fingerstick whole blood, venous whole blood, plasma) are greater than or equal to 95% with the lower boundary of the 95% confidence interval greater than or equal to 90% for all sample types.

19.2 Safety Conclusions

The risk of the device is based on data collected in the clinical study conducted to support PMA approval as described above. Based on the results of the clinical studies, DPP HIV-Syphilis System, when used according to the labeling and in conjunction with other serological and clinical information, is safe to use and poses minimal risk to the patient.

20. BENEFIT-RISK DETERMINATION

The DPP HIV-Syphilis System provides useful information to the patient and healthcare provider on the HIV and Syphilis status of an individual in a point-of-care setting and can serve as an aid in the diagnosis of infection with HIV-1 and HIV-2 and *T. pallidum*. It has the potential, as a rapid test, to lead to diagnosis in a short turnaround time for the test result, enabling counseling and treatment. This is helpful to patients and public health surveillance initiatives.

Risks associated with point-of-care rapid tests relate primarily to its rate of false negative and false positive results. Performance studies have demonstrated that the DPP HIV-Syphilis Assay has a high level of sensitivity and specificity for both HIV and *T. pallidum*. Consequently, the rate of false Reactive and Nonreactive results with the DPP HIV-Syphilis System is very small.

Additionally, all initially HIV reactive and *T. pallidum* reactive specimens require confirmation as per their respective serological testing algorithms, thereby mitigating the risk of false positive results to the patient.

Overall, the information provided by the Applicant indicates that the benefits of the Chembio DPP HIV-Syphilis Assay System outweigh the risks associated with its use.

21. OVERALL CONCLUSIONS

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The data from the nonclinical studies demonstrated acceptable analytical sensitivity, linearity, precision, and analytical specificity of the DPP HIV-Syphilis Assay when used according to the instructions for use as stated in the labeling, the warnings and precautions, and limitations sections of the labeling. The clinical studies and the statistical analysis of clinical data in this application has shown that the DPP HIV-Syphilis Assay is safe and effective when used according to the directions for use in the labeling.

22. APPROVAL SPECIFICATIONS

- Directions for use: See device labeling.
- Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.
- Post-approval Requirements and Restrictions: None.

23. PANEL RECOMMENDATIONS

Not Applicable – This product was not submitted for review by the Blood Products Advisory Committee.

24. FDA/CBER DECISION

The PMA BP180191 is recommended for approval.