Summary Basis for Regulatory Action

Date: August 26, 2019

From: Caren Chancey, Chair of the Review Committee

BLA/STN#: 125670\0

Applicant Name: Bio-Rad Laboratories, Inc.

Date of Submission: December 26, 2017

Complete Response Letter: October 25, 2018

Resubmission: July 1, 2019

MDUFA Goal Date: August 31, 2019

Proprietary Name: Geenius™ HIV 1/2 Supplemental Assay

Established Name (common or usual name): Human Immunodeficiency Virus Types 1 and 2 (Recombinant and Synthetic Peptides)

Intended Use/Indications for 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 serum, or plasma samples (EDTA, lithium heparin, sodium citrate, and CPD) from blood donors. The Geenius™ HIV 1/2 Supplemental Assay is intended for use as an additional, more specific test for human serum and plasma samples with repeatedly reactive results by an FDA licensed blood donor screening test for antibodies to HIV-1/HIV-2. The results of the Geenius™ HIV 1/2 Supplemental Assay are read and interpreted only with the Geenius™ Reader with dedicated software.

Recommended Action: The Review Committee recommends licensure of this product.

Review Office Signatory Authority: Nicole Verdun, 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.**

Table 1. Reviews submitted.

Document Title	Reviewer Name	Document Date
Product Reviews (OBRR/DETTD) • *Clinical* • *Non-Clinical*	 Julia Lathrop Mohan Haleyur Giri Setty	 July 28, 2019 September 27, 2018
Statistical Review • *Clinical*	 Paul Hshieh	 October 2, 2018
CMC Reviews • *CMC (OBRR/DETTD)* • *Facilities Review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	 Mohan Haleyur Giri Setty Cecily Jones Debbie Trout Debbie Trout	 September 27, 2018 October 19, 2018 August 20, 2019 August 6, 2019
Labeling Reviews • *OBRR/DETTD* • *APLB (OCBQ/APLB)*	 Caren Chancey Dana Jones	 August 6, 2019 August 6, 2019
Lot Release Protocol/Testing Plan	Karen Smith Varsha Garnepudi	August 6, 2019 August 5, 2019
Bioresearch Monitoring Review	Haecin Chun	July 18, 2018
Software and Instrumentation	Lisa Simone Nicholas Anderson	August 1, 2018 July 29, 2019

1. Introduction

Bio-Rad Laboratories, Inc., (Redmond, Washington, USA) submitted a Biologics License Application (BLA) for use of the Bio-Rad Geenius™ HIV 1/2 Supplemental Assay as a supplemental assay for blood donor screening.

The sponsor held a pre-submission meeting and discussions (BQ150316) with FDA related to submission for an Intended Use as a supplemental blood donor screening assay, which included a meeting on November 2, 2015 and follow-up email discussion on December 22, 2016. This BLA submission was received December 27, 2017. Communications with the sponsor are described in Table 2.

Table 2. Communications with the sponsor.

Date	Action	Amendment to BL125670
December 27, 2017	CBER Receipt of BLA	
December 29, 2017	Acknowledgment Letter	
January 31, 2018	Information request: software	
February 9, 2018	Response to software IR	\0\1
February 23, 2018	Filing letter with deficiency: lot release	
February 23, 2018	Response to filing deficiency (email)	
March 7, 2018	Information request: BIMO/clinical; software	
March 27, 2018	Response to BIMO/clinical IR	\0\2
April 13, 2018	Information request: software	
April 19, 2018	Information request: DMPQ/CMC	
April 26, 2018	Information request: BIMO/clinical	
April 30, 2018	Response to DMPQ/CMC IR	\0\3
May 14, 2018	Response to BIMO/clinical IR	\0\4
July 5, 2018	Software information, pre-teleconference (email)	
July 10, 2018	Teleconference: Software	
August 1, 2018	Meeting minutes	
August 17, 2018	Information request: clinical/statistical; software	
September 21, 2018	Response to clinical/statistical IR	\0\5
October 25, 2018	Complete response letter: Software; lot release; CMC	
July 1, 2019	Class 1 resubmission	\0\6
July 9, 2019	Information request: DMPQ	
July 10, 2019	Information request: lot release	
July 11, 2019	Acceptance letter: Class 1 resubmission	
July 16, 2019	Response to lot release IR	\0\7
July 17, 2019	Information request: Non-clinical	
July 18, 2019	Response to non-clinical IR	\0\8
July 19, 2019	Information request: Software	
July 22, 2019	Response to software IR	\0\9
July 26, 2019	Response to DMPQ IR	\0\10
August 6, 2019	Information request: Labeling	
August 6, 2019	Response to labeling IR (email)	
August 8, 2019	Teleconference: Lot release	
August 14, 2019	Information request: Labeling	

2. Background

Acquired immunodeficiency syndrome (AIDS) is caused by two types of human immunodeficiency viruses, HIV type 1 (HIV-1) and HIV type 2 (HIV-2). HIV is transmitted by sexual contact, exposure to blood or blood products, and prenatal or perinatal infection of a fetus or newborn. Antibodies to HIV that develop after seroconversion can be detected by donor screening tests. Supplemental (additional, more specific) tests for HIV are used for further testing on donor samples testing reactive by a donor screening test for antibody to HIV-1 and/or HIV-2.

The Geenius™ HIV 1/2 Supplemental Assay is an immunochromatographic assay comprising the Geenius cassette and buffer, assay controls and the Geenius Reader which interprets the assay results. The assay includes antigens for detection of antibody to HIV-1 Group M and O viruses as well as antibody to HIV-2. Currently, there is no FDA-licensed supplemental assay capable of detecting and discriminating HIV-1 and HIV-2 antibodies in blood donor samples.

3. Chemistry, Manufacturing and Controls (CMC)

The manufacture of the Geenius™ HIV 1/2 Supplemental Assay is performed in accordance with Current Good Manufacturing Practices (cGMP) in an environmentally controlled facility.

a) Manufacturing Summary

The Geenius™ HIV 1/2 Supplemental Assay contains:

- Geenius™ HIV 1/2 Test Cassette: Cassette with nitrocellulose membrane containing recombinant HIV-1 and HIV-2 antigens in test area, protein A in control area and colloidal gold protein A in buffer well area
- Running Buffer: Diluent with preservative (< 0.1% sodium azide)

The kits manufactured for the donor screening Intended Use will be identical to those manufactured for the diagnostic Intended Use; however, the kits will have separate Instructions for Use and will be labeled with a different catalog number (#72480). (Note: the Geenius™ HIV 1/2 controls are approved under BP140120 and are not included in this BLA.)

In vitro substance and in vitro product

The in vitro substance for the Geenius cassette consists of (b) (4) synthetic peptides, developed by Bio-Rad and produced by two qualified suppliers and two recombinant proteins, developed by Bio-Rad and produced at Bio-Rad's (b) (4) manufacturing facility. Additionally, a protein A stock solution is prepared for use in manufacture of the cassette control test line, which is printed on test line 7. The in vitro product consists of the assembled cassette and its components as well as the running buffer. The content of the submission has been reviewed and found to be acceptable.

In process testing and specifications

The analytical methods and their validations and/or qualifications reviewed for the Geenius™ HIV 1/2 Supplemental Assay kit were found to be adequate for their intended uses.

Release testing and specifications

The Geenius™ HIV 1/2 Supplemental Assay is packaged as a kit containing 20 cassettes and one buffer reagent bottle.

The performance of each lot of the Geenius™ HIV 1/2 Supplemental assay is evaluated with sensitivity and specificity members. These QC sensitivity members have been developed to contain moderately positive and weakly positive HIV-1 Ab, HIV-2 Ab, HIV-1 Group O Ab, as well as negative members. The performance of each lot of the Geenius™ HIV 1/2 Supplemental assay is also evaluated against CBER Lot Release panels for HIV-1 and HIV-2 antibody. Additionally, (b) (4) lots of Geenius™ HIV 1/2 Controls are used to check the performance of each lot of assembled Geenius™ HIV 1/2 Supplemental Assay kits. The content of the submission has been reviewed and found to be acceptable.

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Geenius™ HIV 1/2 Supplemental Assay are listed in the table below. The activities performed, and inspectional histories are noted in the table.

Table 3. Manufacturing Facilities Table for Geenius™ HIV 1/2 Supplemental Assay.

Name/Address	FEI number	Inspection/ Waiver	Justification/ Results
Final Kit Manufacturer and Final Kit Release Testing Bio-Rad Laboratories, Inc. (b) (4)	(b) (4)	Waived	Team Biologics (b) (4) VAI
Component Manufacture (filling, capping, labeling of kit components) *Geenius cassette manufacturing* *Preparation and testing of bulk buffer and controls* Bio-Rad Laboratories (b) (4)	(b) (4)	Waived	ORA (b) (4) NAI

Team Biologics conducted a surveillance inspection at Bio-Rad Laboratories, Inc. in (b) (4) and a Form FDA 483 was issued to the firm at the close of the inspection. All inspectional issues were resolved, and the inspection was classified as voluntary action indicated (VAI). ORA performed a surveillance inspection of Bio-Rad Laboratories in (b) (4) in (b) (4) and no Form FDA 483 was issued, and the inspection was classified as no action indicated (NAI).

d) Environmental Assessment

The BLA included a request for categorical exclusion from an environmental assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Container Closure

N/A

4. Software and Instrumentation

The following is a summary overview of software, instrumentation and risk management information provided to support a reasonable assurance that the device is safe and effective for its intended uses and conditions of use.

a) Versioning:
The Geenius system software for launch will be v2.0.

b) Device Description:
The Geenius HIV 1/2 Supplemental Assay is composed of the Geenius Reader, a sample cartridge (cassette) and the system software.

Geenius Cassette: The Geenius cassette 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. The assay uses two HIV-2 antigens (gp36 and gp140) and four HIV-1 antigens (p31, gp160, p24 and gp41), one of which (gp41) is reactive with antibodies to HIV-1 Groups M and O.
The sample is applied to the Sample + Buffer well and allowed to migrate onto the test strip. Additional buffer is then added to the Buffer well, which causes the specimens and reagents to flow laterally and facilitates the binding of antibodies to the antigens. In a reactive sample, anti-HIV-1/2 antibodies are captured by the HIV-1 and/or HIV-2 antigens immobilized in the Test area (Table 4).

Table 4. HIV-1 and HIV-2 antigen bands in the Geenius cassette.

Band ID	Peptide/Protein	Description
Band 1	gp36	HIV-2 envelope peptide
Band 2	gp140	HIV-2 envelope peptides
Band 3	p31	HIV-1 polymerase peptide
Band 4	gp160	HIV-1 envelope recombinant protein
Band 5	p24	HIV-1 gag (core) recombinant protein
Band 6	gp41	HIV-1 group M and O envelope peptides
Band 7	Ctrl	Protein A control

The protein A-colloidal gold binds to the captured antibodies, causing development of pink/purple lines. When there are no HIV antibodies, there are no pink/purple lines in the test area. The sample continues to migrate through the membrane to the control area, which contains immobilized Protein A to capture remaining antibody present in the sample regardless of specificity. Captured antibody is then detected by the Protein A-colloidal gold and a pink/purple line develops in the control area. This built-in procedural control provides evidence that the test was performed properly and that the sample and reagents have migrated through the cassette. Assay results are read only by the Geenius Reader, with interpretation by the Geenius Software, based on predefined cutoffs for each of the HIV-1 and HIV-2 bands. The Geenius Reader detects reactive bands on a cassette using an onboard camera. The associated Geenius software then evaluates the bands and determines the test result according to predefined rules (Table 5).

Table 5. Results interpretation for the Geenius HIV 1/2 supplemental assay.

Interpretation	Control	HIV-1	HIV-2
Invalid	Not present OR	Any band invalid	Any band invalid
HIV-negative	Present	Negative	Negative
HIV-1 positive	Present	Positive	Negative
HIV-1 indeterminate	Present	Bands present but does not meet criteria for positive	Negative
HIV-2 positive	Present	Negative	Positive (Both gp140 and gp36)
HIV-2 indeterminate	Present	Negative	Either gp140 or gp36 present
HIV-2 positive with HIV-1 cross-reactivity	Present	≤1 HIV-1 envelope band	Both gp140 and gp36
HIV untypable	Present	Positive	Positive
HIV indeterminate	Present	Indeterminate	Indeterminate

Geenius Reader:
The Geenius Reader is used to read the Geenius cassette. Reactive bands on a cassette are detected by the onboard camera. The associated Geenius software performs the detection data analysis and the results interpretation according to predefined algorithms.

The Geenius software generates a worklist from the samples identified and captured manually by the user into the worklist view of the software. The software then communicates with the Reader and calibrates lighting, performs the test device reading, analyzes the image taken by the Reader's camera and provides the result. It can print reports, and, if the result is validated by user, the result can be transmitted to the LIS and archived.

Geenius Software:
The Geenius software runs on an external PC. The PC and the Geenius Reader instrument are separate devices. The software allows the user to connect to the instrument. The user interacts with the software through a keyboard and a mouse. The software interacts with the instruments through the USB port connection. The Geenius software interacts with the Reader and the image analysis module through dynamic link libraries (DLLs).

The control of the Geenius device by software is as follows. Geenius software generates a worklist, communicates with the Reader, controls it and performs the test device reading. It then collects and analyzes the data, prints the reports if needed, and transmits the validated results to the LIS. The main components controlled by the Geenius software are: LEDs, camera, and sensors. The Geenius software can also control external printers.

• Geenius software controls the Geenius Reader. Hardware communication between the Reader and the PC is established via a USB cable and the software GUI.
• Geenius software can't run a cassette if a Reader is not connected.
• Geenius software, when launched, sets the Reader to calibrate light intensity and exposure time before it starts running any cassettes.
• Geenius software returns the Geenius reader status and collects images that are read by the Reader's camera.
• Geenius software analyzes each image with the Picture Analyzer module for band detection of tests supported by the Geenius Software application.

The operating environment includes the following: Geenius software running on a PC with Windows 7 Pro 32 or 64 bit. Database management uses SQL Server 2014 Express. Bidirectional communication capability i.e. the ability to import work lists from the LIS (Laboratory Information System) and export results to the LIS via a LAN (Ethernet) Port on the computer. Data export is via CSV or ASTM formats.

Assay specific software: All information necessary for reading and analyzing the cassettes, specific to the HIV 1/2 assay, is contained in the Assay Protocol File (APF). An Assay Protocol File editor is available for R&D and Marketing users only to create, edit and release APFs per test or type of cassette. Tests have the following properties: Test Name, Test Description, Kit Lot ID Format (future use), Test Version, Test ID, Test Window (test window location dimensional sizes), Test Bands (properties of regular and control hands), and Picture Analyzer (border and test window picture parameters).

c) Risk Management:

Requirements of the version 2.0 of the Geenius software and the list of known residual anomalies were analyzed and the risks identified were added to the risk analysis. In the traceability matrix for software v2.0, all verification tests for which a risk was identified were passed. 159 items applicable to the U.S. configuration of the software are listed in the risk analysis. For 49 of these items, no hazard or hazardous situation has been identified.

One residual risk is unacceptable, with a frequency level of 4 and a severity level of 2. It corresponds to item RA-168 and residual anomaly STA02771. This anomaly shows that it is necessary to click twice on the print button in the windows dialog box to start the printing. The associated risk is a risk of user discomfort. Considering the report can be printed with an easy to use workaround (double clicking), the benefit/risk analysis is favorable, and the correction of the anomaly has been postponed to a future version of the software. All other residual risks related to the software are acceptable. All residual risks related to cybersecurity are acceptable. All residual risks related to OTS software are acceptable.

In the risk analysis of hardware, 102 items are listed. For 22 of these items, no hazard or hazardous situation has been identified. All residual risks related to the hardware are acceptable.

d) Unresolved Anomalies:

The list of unresolved anomalies includes one item with a potential impact on patient safety related to a delayed result. This item is associated with an external barcode scanner deleting a space character, preventing the result from being automatically associated with a sample ID from a user-created worklist. The sponsor states that the risk is user discomfort as it would require the user to manually link the result to the sample. The sample ID cannot be misinterpreted as a different valid sample ID by the system. The initial risk evaluation is low, and the frequency is unlikely. The sponsor states that the current risk mitigation includes additional information in the user manual, with a future software update to verify the sample ID format prior to testing. If the sample ID contains unallowable characters or formats, the cartridge will be rejected, and an information message will be displayed. The current risk of this anomaly is considered low and acceptable according to the sponsor's risk management process.

e) Testing:

Design verification was performed to confirm the design elements meet the specified requirements and includes verification of the effectiveness of risk control measures for potential causes of failure modes. This included software verification, software validation, and system integration.

f) Development Management:

The software development activities included establishing detailed software requirements, linking requirements with associate verification tests, verification and validation testing, defect tracking, configuration management and maintenance activities to ensure the software conforms to user needs and intended uses.

g) Software Major Review Issues

During review of the software documentation, multiple deficiencies were noted related to cybersecurity, risk management, and documentation. In discussions with FDA, the sponsor noted that they had a new version of the Geenius system software (v2.0) under development, in which many, but not all, of the deficiencies could be resolved. FDA held a teleconference with the sponsor on July 10, 2018 to discuss: which deficiencies could be resolved by updating documentation for the current software, v1.3; which additional deficiencies could be resolved in v2.0; and which deficiencies could not be resolved in v2.0. Addressing deficiencies that could not be resolved in v2.0, as it was already under development, would require halting work on v2.0 and beginning work on a new version. During the teleconference, Bio-Rad and FDA agreed that the deficiencies posing the greatest risk could be addressed in v2.0, which was expected to be ready in early 2019.

1. It was noted that the external software SQL Server 2005 Express, which is used for database management, had reached product end of life in 2016; thus, no application fixes or security patches were being provided and the outdated software posed a security risk. In an Information Request sent March 7, 2018, FDA requested that the sponsor provide a strategy to address current security risks and migrate away from the insecure software. In their response on March 27, 2018, the sponsor stated that Geenius system software v2.0 would utilize a more recent software, Microsoft SQL Server 2014 Service Pack 2 Express. The response was considered acceptable.

   The following summarized deficiencies were initially sent to the sponsor as part of an IR on April 13, 2018, updated following the teleconference of July 10, 2018, and included in the CR letter sent October 25, 2018. The resolution for each was included in the July 1, 2019 response to the CR letter, BL125670\0\6.

2. Issues with the risk management procedures and documentation in the Geenius software and instrument manual were noted, including:
   - multiple instances of failure to align with the requirements of ISO 14971;
   - the scope of the device hazard analysis excluding risks associated with the APF or with the proposed Intended Use for donor screening;
   - excessive reliance on labeling or user intervention in risk mitigations;
   - mitigations relying on a supervisor responding to a risk rather than a regular user;
   - lack of a usability risk analysis;
   - lack of traceability between the hazard analysis and user manual warnings; and
   - lack of information on risks associated with warnings provided in the user manual.

   FDA asked for updated risk management documentation addressing the issues noted above. In their response, the sponsor provided the requested documentation for Geenius software v2.0. The sponsor also noted that no risks for which mitigations are reliant on user intervention relate to reporting of assay results. The response was considered acceptable.

3. Multiple issues were noted with cybersecurity regarding the Geenius Reader and its software, for which FDA requested additional documentation and updates to the user manual. These included:
   - missing cybersecurity risk management information;

- no requirement for use of secure, individual accounts at the appropriate user level so that user-intervention based mitigations could be tracked; and
- security vulnerability for a restored Geenius database which could be accessed via old passwords, even when those were expired or potentially compromised.

In their response, the sponsor provided the requested documentation for software v2.0 and the response was considered acceptable.

4. The Device Hazard Analysis provided in the submission described high severity risks related to situations where the sample barcode or Geenius cassette barcode was missing or could not be read by the Geenius Reader. The mitigations developed relied heavily on user intervention, but it was unclear whether they were adequate to prevent harm, and the risks associated with manual barcode entry were not sufficiently described for users in the user manual. FDA requested that, where possible, the sponsor provide protective measures, such as a checkbox confirming visual verification of correct barcode entry, rather than relying on user intervention and provide additional information to users regarding risks and needed safety precautions. This issue was discussed during the July 10, 2018 teleconference where the sponsor noted that the User Manual could be updated for either the current software version or v2.0 under development with the additional information requested, but that software-based protective measures could not be added until a later software version. FDA agreed that the software-based protective measures could be deferred to the next update after v2.0. In the July 1, 2019 response, the sponsor provided an updated User Manual with the additional precautions, revised user procedures and risk information. The response was considered acceptable.

5. The Unresolved Anomalies list provided by the sponsor for software v1.2 included several anomalies and workarounds which were several years old. FDA requested updated information on the failed tests leading to detection of each anomaly, the occurrence of each issue since v1.2 was released, and corrective plans for each. In their response, the sponsor provided updated information for two anomalies and stated that four others were no longer relevant for software v2.o. The response was considered acceptable.

6. Other issues were noted in the Geenius risk documentation and User Manual provided in the submission, including:
    - lack of updated information for customers on known OTS software defects;
    - lack of verification testing documentation and risk documentation for database restoration and archival database usage;
    - lack of design control documentation for the firmware modules which are underlying components of the Geenius software;
    - lack of information regarding APF versioning and revision history;

- lack of documentation for risks of connecting to a computer operating in battery mode or via a USB hub;
- conflicting information on use of customer-provided computers with the Geenius Reader; and
- use of Windows XP, which reached end-of-life in 2014, with the Geenius software.

In their response, the sponsor provided the requested documentation. The sponsor clarified that a dedicated PC is supplied for all Geenius Readers sold in the U.S., and that Windows XP is not a permitted operating system for use with Geenius software v2.0. The response was considered acceptable.

5. Analytical Studies

Because the assay design and kit components for the Geenius™ HIV 1/2 Supplemental Assay are the same as were approved for diagnostic use under BP140120, the analytical/non-clinical studies previously performed to support that application were referenced in this application. Two additional studies supporting the performance of the Geenius™ HIV 1/2 Supplemental Assay with CPD (Citrate Phosphate Dextrose) anticoagulant typically used with blood donor samples were included to support the proposed intended use as a supplementary assay for blood donor screening. The analytical/non-clinical studies performed are described below in sections 5.a – 5.k.

The results described below represent the data as analyzed with software v2.0, the version intended for licensure.

Note that many of the non-clinical studies for the diagnostic test version of this supplemental assay were done with (b) (4) collected with EDTA or lithium heparin anticoagulants as a matrix. However, (b) (4) is not included as a matrix for the proposed Intended Use for blood donor screening in this BLA. Therefore, only results with serum or plasma will be summarized in this SBRA. Unless otherwise noted, for studies utilizing spiking, spike volumes were designed to produce a positive status with all HIV-1 and HIV-2 bands at a low intensity level. Agreement between conditions was assessed at the level of band pattern and final result interpretation.

a) Sample Matrix (anticoagulant)

This study was performed to compare the performance of the Geenius™ HIV 1/2 Supplemental Assay using samples collected as serum (gel or dry tubes), or plasma (EDTA(b) (4), lithium heparin or sodium citrate anticoagulants). Additional testing was performed in the same manner to validate CPD plasma (plasma from (b) (4) bags collected with CPD), which is a sample matrix typically tested for blood donor screening. Samples were prepared by spiking negative paired samples with either HIV-1 or HIV-2 Ab-positive plasma. Serum collected in gel SSTs was used as the reference condition for serum collected in dry tubes, EDTA-

(b) (4) plasma and CPD plasma; EDTA(b) (4) plasma was used as reference for heparin and citrate plasma. For dry serum tubes, EDTA plasma, lithium heparin plasma, sodium citrate plasma and CPD plasma, 100% (50/50) agreement was observed between the test and reference conditions for all negative and HIV-positive specimens. All tests for spiked and unspiked samples in all matrices yielded the expected results. The sponsor reported that the observed (b) (4) rate of indeterminate results in negative samples was below the indeterminate rate of (b) (4) found in prior internal studies. The results demonstrated acceptable performance in all matrices tested.

b) Sample Shipping and Storage

To assess the stability of fresh serum samples (gel SST) or plasma samples collected in EDTA(b) (4), lithium heparin, sodium citrate or CPD under a variety of storage conditions including ambient shipping conditions up to (b) (4), the sponsor collected paired serum and plasma samples from donors. For each set of donors, samples were tested unspiked or spiked with HIV-1 Ab or HIV-2 Ab. Spiked and unspiked specimens were split into aliquots which were tested at three different temperature storage conditions: 2-8°C, 18-30°C (b) (4) , or subjected to a maximum of 5 freeze/thaw cycles. For serum and EDTA plasma, all negative and HIV-1 spiked specimens gave correct results after up to (b) (4) days storage under all (b) (4) temperature conditions (2-8°C, 18-30°C (b) (4)). Two HIV-2 spiked EDTA plasma specimens generated negative results at one storage point each; remade and retested specimens for each produced correct results at each time point. All tested heparin and citrate plasma samples, spiked and unspiked, yielded the expected results before and after storage for: (b) (4) days at 2-8°C; (b) (4) days at 18-30°C; (b) (4) ; or 5 freeze/thaw cycles. All tested CPD plasma samples, spiked and unspiked, yielded the expected results before and after storage for: (b) (4) days at 2-8°C; (b) (4) days at 18-30°C; (b) (4) ; or 5 freeze/thaw cycles. The sponsor noted that some HIV-2 spiked samples gave HIV-1 indeterminate band results that did not change the final sample interpretation of HIV-2 positive. All negative, HIV-1 and HIV-2 spiked specimens generated correct results after five freeze/thaw cycles for all matrices tested. The results demonstrated acceptable performance for each tested condition for storage of serum and plasma specimens, supporting the inclusion of these conditions in the labeling.

c) Cross-reactivity

Cross-reactivity of the Geenius™ HIV 1/2 Supplemental Assay was assessed using presumed HIV-1 negative specimens positive for potentially cross-reactive conditions (listed in Table 6), both unspiked and spiked with HIV-1 or HIV-2 Ab.

Table 6. Conditions tested for cross-reactivity.

Infectious organism positives (#)	Autoimmune conditions (#)	Other health conditions (#)
HTLV I/II (10)	SLE (Lupus) patients (6)	Rheumatoid factor positive (10)
HCV Ab (10)	Scleroderma patients (2)	Myeloma patient (5)
HBsAg (10)	Sjogrens patients (2)	HAMA positive (10)
HAV Ab (10)	MCTD patients (2)	Multi-transfused patients (10)
CMV Ab (10)	ANA patients (3)	Dialysis patients (10)
EBV Ab (10)		Hemophilia patients (10)
HSV Ab (10)		Cancer patients (5)
Rubella Ab (10)		Cirrhosis patients (5)
Toxoplasmosis Ab (5)		Pregnant (HCG+) women (10)
Influenza vaccine (5)		Multiparous women (5)
Malaria Ab (16/13*)		
Yeast (Candida) Ab (10)		
Vaccinia Ab (10)		
Syphilis Ab (10)		

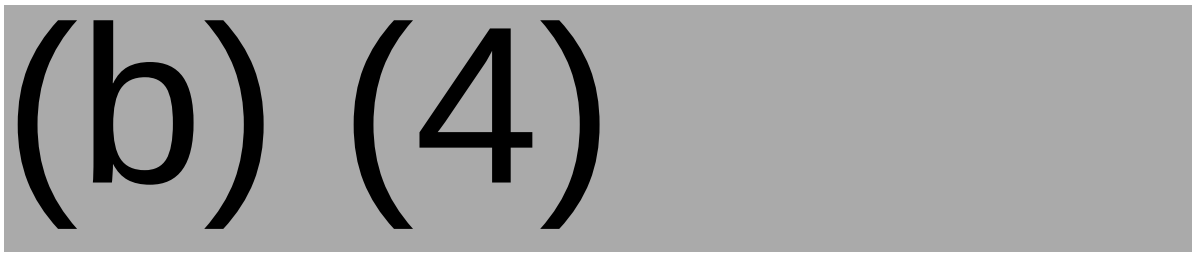
*3 Malaria Ab-positive specimens were not tested as spiked specimens.

No false positives (0/227) were observed when testing unspiked potentially cross-reactive specimens with the Geenius™ HIV 1/2 Supplemental Assay, with an indeterminate rate of 1.8% (4/227) on initial testing and an invalid rate of 1.7% (4/231). Indeterminates were identified in the HCV, Malaria and HBsAg groups.

Reactivity of the Geenius™ HIV 1/2 Supplemental Assay with HIV antibody-spiked potentially cross-reactive specimens was 100% (228/228). The results demonstrated acceptable performance of the assay in the presence of potential cross-reactants.

d) Interfering Substances

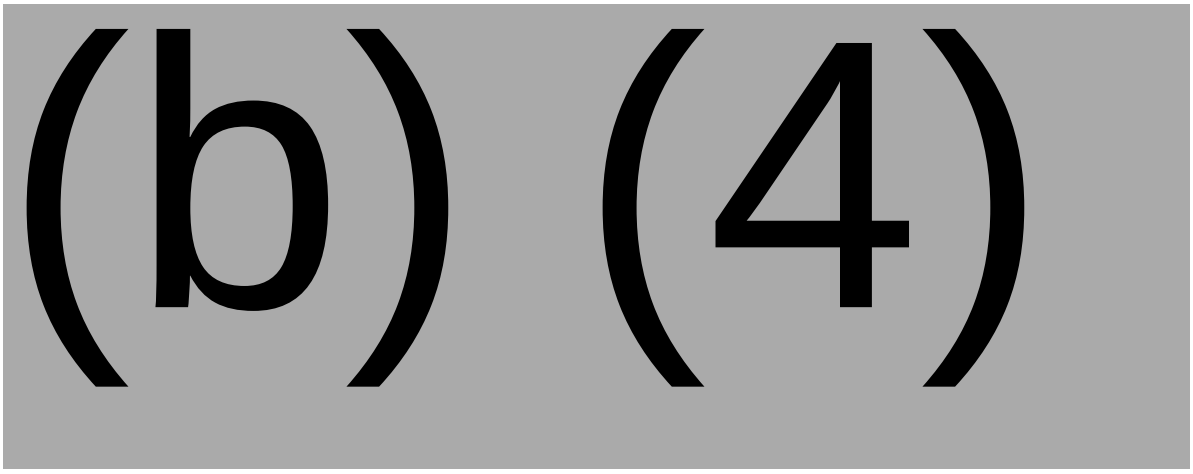
The performance of the Geenius™ HIV 1/2 Supplemental Assay with samples containing high levels of potentially interfering substances was performed in the same manner as described above for cross-reactivity. The potentially interfering substances and tested concentrations are listed in Table 7.



All HIV-negative, HIV-1 Ab spiked and HIV-2 Ab spiked samples yielded correct results both with and without potentially interfering substances. The data provided and reviewed demonstrated acceptable performance of the Geenius™ HIV 1/2 Supplemental Assay in the presence of the tested substances.

e) Sample Microbial Contamination Interference

The performance of the Geenius™ HIV 1/2 Supplemental Assay with microbially contaminated specimens was assessed by preparing (b) (4) HIV-negative serum and plasma specimens, unspiked and spiked with HIV-1 Ab positive or HIV-2 Ab positive plasma. Each positive or negative (b) (4) was then divided into (b) (4) aliquots and spiked with (b) (4) potentially interfering bacterial contaminants, or (b) (4) growth media controls (Table 8).



All HIV-negative, HIV-1 Ab spiked and HIV-2 Ab spiked samples yielded correct results both with and without potentially interfering substances, demonstrating that the performance of the Geenius™ HIV 1/2 Supplemental Assay was not affected by the tested substances. However, one of (b) (4) replicates of the HIV-2 spiked plasma contaminated with (b) (4) produced a result of HIV-2 positive with HIV-1 cross-reactivity due to the presence of p31 and gp160 bands at low intensity. The sponsor concluded that the result was not due to bacterial interference because it only occurred in one cassette. However, no alternate cause for the cross-reactive bands was suggested or demonstrated; thus, bacterial interference as a source of the HIV-1 cross-reactivity could not be ruled out. The observed cross-reactivity would not change results for HIV supplemental donor screening and was considered acceptable by the committee. The data provided

and reviewed demonstrated acceptable performance of the Geenius™ HIV 1/2 Supplemental Assay in the presence of the tested substances.

f) Hook Effect

Performance of the Geenius™ HIV 1/2 Supplemental Assay was assessed with high titer specimens in order to determine whether a hook effect (a reduction in assay signal observed when samples of increasing high titer are assayed) would be observed. Two strong positive (based on reference assays) HIV-1 and HIV-2 specimens were tested with the Geenius™ HIV 1/2 Supplemental Assay neat and over a range of (b) (4) -fold dilutions. Each of the four specimens tested showed decreasing band intensities and interpretation changes from positive to negative down the dilution series; thus, no hook effect was observed when testing with the Geenius™ HIV 1/2 Supplemental Assay.

g) Sensitivity with HIV-1 Seroconversion Panels

This study was performed to assess the performance of the Geenius™ HIV 1/2 Supplemental Assay on 32 HIV-1 seroconversion panels, in comparison to an FDA-approved HIV-1 confirmatory western blot assay (the GS HIV-1 Western Blot, also from Bio-Rad). The detection of the first positive bleed was at an earlier time point on 21.9% (7/32), at a later timepoint on 9.4% (3/32), and at the same time on 59.4% (19/32) of the panels with the Geenius as compared to the western blot. The 32 seroconversion panels comprised a total of 154 individual seroconversion samples, 80 of which were early seroconversion samples. Results of testing the 154 individual samples are shown in Table 9.

Table 9. Sensitivity with 154 seroconversion samples.

	Geenius™ HIV 1/2 Supplemental Assay	**GS HIV-1 Western Blot**
HIV-1 negative	76 (49.4%)	67 (43.5%)
HIV-1 indeterminate	19 (12.3%)	34 (22.1%)
HIV-1 positive	59 (38.3%)	53 (34.4%)

Of the 80 early seroconversion samples, 5.0% (4/80) were positive with the Geenius™ HIV 1/2 Supplemental Assay as compared to none with the GS HIV-1 Western Blot (Table 10).

Table 10. Sensitivity with 80 early seroconversion samples.

	Geenius™ HIV 1/2 Supplemental Assay	**GS HIV-1 Western Blot**
HIV-1 negative	65 (81.3%)	58 (72.5%)
HIV-1 indeterminate	11 (13.8%)	22 (27.5%)
HIV-1 positive	4* (5.0%)	0 (0%)

*All four samples which were HIV-1 positive using the Geenius™ were HIV-1 indeterminate using the western blot.

The data provided and reviewed demonstrated acceptable performance, supporting that the Geenius™ HIV 1/2 Supplemental Assay performed as well with seroconversion panels as currently available assays.

h) Analytical Sensitivity with HIV-1 Group M Subtypes and Group O Samples

Sensitivity of the Geenius™ HIV 1/2 Supplemental Assay with different HIV-1 subtypes and groups was assessed by testing 87 samples representing group O (n=5), group M subtypes B (n=9) and non-B (n=36), as well as circulating recombinant forms (CRF) (n=37). Testing of all of the samples yielded a correct HIV-1 positive result, with no invalid or indeterminate samples, with a sensitivity of 100% (87/87) and 95% CI (95.85-100). The results demonstrated acceptable performance supporting the use of the Geenius™ HIV 1/2 Supplemental Assay with different HIV-1 subtypes.

i) Precision and Repeatability (analytical)

This study was performed to establish the same-day repeatability and precision within runs and between days of the Geenius™ HIV 1/2 Supplemental Assay with serum (b) (4) samples. A (b) (4)-member serum panel was prepared by spiking (b) (4) HIV-negative specimens with HIV-1 or HIV-2 antibodies to result in negative, indeterminate and low positive panel members. Repeatability was assessed by testing the panels (b) (4) times in a single day. Precision was assessed by testing in (b) (4) runs per day for (b) (4) days. The sponsor reported 100% agreement for all samples for the repeatability, within-run and between-run precision testing. The data provided and reviewed demonstrated acceptable performance in regard to precision and repeatability in the non-clinical setting.

j) Robustness and Customer Abuse

This study was performed to establish the robustness and performance of the Geenius™ HIV 1/2 Supplemental Assay under changes in operating conditions (robustness) as well as use outside of normal operating conditions (customer abuse). Panels were prepared by spiking serum/plasma with HIV-1 and HIV-2 positive. The conditions assessed for robustness and/or customer abuse included sample volume, buffer volumes for steps 1 and 2, wait times for each incubation step, incubation temperature, humidity exposure, light exposure, sample/reagent addition in incorrect well, use of incorrect kit pipette (serum/plasma vs. (b) (4)) or use of control pipette for samples. The results showed that all robustness conditions tested as well as some customer abuse conditions still generated valid, correct results. The customer abuse conditions that led to invalid or incorrect results were noted on the package labeling. One customer abuse condition (use of 5 µl pipette for 15 µl (b) (4) sample) produced valid and correct results, but cautions were still added to the labeling because the condition resulted in reduced band intensity which could cause early infections to be missed. The data provided and reviewed demonstrated acceptable performance

of the assay and supported appropriate labeling recommendations and cautions for incorrect use.

k) Stability

Stability of the Geenius™ HIV 1/2 Supplemental Assay was evaluated using a (b) (4) member stability panel comprised of HIV-1 high and low positive samples, HIV-2 high and low positive samples, an HIV-1 Group O positive sample and a negative sample. Test kits were tested after storage at 2-8° C and 30(b) (4)° C at the following time points: Time 0, 3 months, 6 months, 9 months, 12 months, 13 months, 18 months, 20 months, 24 months (b) (4) . Open vial stability for the Geenius running buffer were also assessed, using the same storage conditions and time points as the kit stability protocol.

The stability of the Geenius™ HIV 1/2 Supplemental Assay was also evaluated under conditions of shipping stress, using the same stability panel, over a period of (b) (4) days under varying temperature (-20°C, 2-8° C, room temperature, (b) (4) stress conditions. Stressed kits were then stored as for the standard stability protocol and results compared to the stability results from the stored kits from the same lots which were not stressed. Data from these studies support a 24-month dating period for the components of the Geenius™ HIV 1/2 Supplemental Assay, with the expiration of the assembled kit based on the component with the shortest dating period.

Overall, the non-clinical/analytical studies were performed appropriately, and no substantial issues were raised during committee review.

6. Clinical Studies

a) Clinical Program

As agreed in BQ150316, a new clinical study was performed to support the performance of the Geenius™ HIV 1/2 Supplemental Assay for the proposed Intended Use as a supplemental test for donor-screening. Additional clinical studies supporting the diagnostic Intended Use were also included in the current BLA as supporting data. Results presented here are those analyzed using Geenius software v2.0/APF 2.0, the version intended for licensure.

i. BLA clinical studies

Evaluation of the performance of the Geenius™ HIV 1/2 Supplemental Assay in follow-up testing of serum and plasma from blood donors was conducted under IND 17463. All Geenius testing was performed at a single site, using unlinked and de-identified remnant samples from multiple donor centers across the U.S., repository samples, or samples purchased from commercial vendors. Additional testing for all samples was performed using FDA-approved comparator assays (Fluorognost HIV-IFA and Bio-Rad GS HIV-2 EIA). Discrepancies between the investigational assay and the comparator assay were resolved by testing samples using the Multispot HIV-1/HIV-2 assay. Three lots of Geenius™ HIV 1/2

Supplemental Assay kits and three lots of Geenius controls were used in the study, with test samples divided approximately evenly between the three lots. Performance of Geenius™ HIV 1/2 Supplemental Assay was evaluated in three populations: normal donors; HIV EIA repeat reactive, non-confirmed donors; and known HIV positive donors. Sample numbers and sources for each study population are shown in Table 11.

Table 11. Sample numbers and sources for clinical studies.

Population	Serum	Plasma	Totals
Normal Donors	100 ARC	100 Plasma Donor Center	200
HIV EIA Repeat Reactive – Non-Confirmed Blood Donors	50 ARC Repository	50 ARC Repository	100
Known HIV-Positive Blood Donors	100 ARC Repository	100 ARC Repository	200
Total	**250**	**250**	**500**

Clinical Specificity in Normal Donors

The clinical specificity of the Geenius™ HIV 1/2 Supplemental Assay was assessed in 100 serum samples from normal blood donors and 100 plasma samples collected from normal plasma donors (Table 12). Samples from normal donors were all negative in FDA-licensed donor screening HIV-1/HIV-2 EIA tests.

Table 12. Specificity results: Normal donors.

Matrix	Number	Geenius™ HIV 1/2 Results (Neg/Ind/Pos)	HIV-1 IFA Results (Neg/Ind/Pos)	GS HIV-2 EIA Results (NR/RR)
Serum	100	97/3[1]/0	99/1[4]/0	100/0
Plasma	100	94/6[2]/0	100/0/0	99/1[4]
Total	200	191/9[3]/0	199/1[4]/0	199/1[4]

[1] One sample was HIV Indeterminate and two samples were HIV-1 Indeterminate. Two of the three samples were Negative on the Multispot HIV-1/HIV-2 Rapid Test. One sample was HIV-1 Indeterminate on the Multispot HIV-1/HIV-2 Rapid Test.

[2] Five samples were HIV-2 Indeterminate and one sample was HIV-1 indeterminate. All these samples were Negative on the Multispot HIV-1/HIV-2 Rapid Test.

[3] Five samples were HIV-2 Indeterminate, three samples were HIV-1 Indeterminate and one sample was HIV Indeterminate.

[4] Negative on the Multispot HIV-1/HIV-2 Rapid Test.

No false positives were observed in the study, and the overall indeterminate rate in the normal donor population for the Geenius™ HIV 1/2 Supplemental Assay was 4.50% (9/200) for both sample types combined. The sponsor noted that these samples would not typically be tested using the Geenius™ HIV 1/2 Supplemental Assay because they were negative on an FDA-licensed HIV-1/HIV-2 EIA donor screening assay. Because samples with indeterminate results are neither negative nor false positive, no specificity calculation is presented for the low risk samples, and the labeling includes the descriptive statistics.

Clinical Specificity in non-confirmed EIA repeat reactive donors

The clinical specificity of the Geenius™ HIV 1/2 Supplemental Assay was assessed in 50 serum samples and 50 plasma samples from the ARC sample repository. These false reactive samples were initially reactive when screened on either of two different FDA-licensed HIV donor screening tests but failed to confirm when tested with the HIV-1 Western Blot or HIV-2 EIA (Table 13).

Table 13. Results for repeat-reactive/not confirmed blood donors.

Matrix	Repeat reactive	Manufacturer of initial test (N tested)	Geenius HIV 1/2 NEG/IND/POS
Serum	50	Abbott PRISM HIV O Plus (N = 30)	27/3[1]/0
Serum	50	GS HIV-1/HIV-2 PLUS O EIA (N = 20)	20/0/0
Plasma	50	Abbott PRISM HIV O Plus (N = 39)	39/0/0
Plasma	50	GS HIV-1/HIV-2 PLUS O EIA (N = 11)	10/1[2]/0
Total	100	100	96/4[3]/0

[1] Three samples were HIV-2 Indeterminate when tested on Geenius™ HIV 1/2 Supplemental Assay. These samples were Negative on the Multispot HIV-1/HIV-2 Rapid Test.

[2] One sample) was HIV-2 Indeterminate when tested on Geenius™ HIV 1/2 Supplemental Assay. This sample was Negative on the Multispot HIV-1/HIV-2 Rapid Test.

[3] Four samples were HIV-2 Indeterminate when tested on Geenius™ HIV 1/2 Supplemental Assay. These samples were Negative on the Multispot HIV-1/HIV-2 Rapid Test.

No false positives were observed in the study, and the overall indeterminate rate in the repeat reactive donor population for the Geenius™ HIV 1/2 Supplemental Assay was 4% (4/100). Because samples with indeterminate results are neither negative nor false positive, no specificity calculation is presented for the repeat reactive samples, and the labeling includes the descriptive statistics.

Clinical Sensitivity in known HIV-positive blood donors

The clinical sensitivity of the Geenius™ HIV 1/2 Supplemental Assay in known HIV-positive blood donors was assessed using 100 serum samples and 100 plasma samples from the ARC sample repository (Table 14).

Table 14. Sensitivity in HIV-1 known-positive samples.

Matrix	# tested	Geenius™ HIV-1 POS/HIV-2 POS/IND/NEG	Geenius™ HIV 1/2 Sensitivity	Geenius™ HIV 1/2 95% CI	HIV-1 IFA POS/IND/ NEG
Serum	100	100/0/0/0	100%	96.3–100%	94/1*/5*
Plasma	100	100/0/0/0	100%	96.3–100%	98/0/2*
Total	200	200/0/0/0	100%	98.12–100%	192/1*/7*

* These samples were HIV-1 Positive on the Multispot HIV-1/HIV-2 Rapid Test and Positive on Procleix UltrioPlus TMA assay in historical data.

The GS HIV-2 EIA package insert states "Most specimens (50–90%) that are positive for antibody to HIV-1 will also react in the GS HIV-2 EIA due to cross reactivity primarily between the core (*gag*) and polymerase (*pol*) proteins of the two viruses. Samples with repeatedly reactive results must be investigated further by additional more specific or supplemental tests." 154 of the 200 known HIV-1 positive samples were repeatedly reactive with the GS HIV-2 EIA. The Multispot HIV-1/HIV-2 Rapid Test was performed on the 154 GS HIV-2 EIA repeat reactive samples to resolve the discrepancy and all 154 samples tested HIV-2 negative. The data are presented below in Table 15.

Table 15. Sensitivity for HIV-1 positive samples compared with GS HIV-2 EIA, with Multi-Spot HIV-1/HIV-2 Rapid Test.

Matrix	# tested	Geenius™ HIV-1 POS/HIV-2 POS/ IND/NEG	GS HIV-2 EIA RR/NR	Multispot HIV-1 POS/HIV-2 POS/ IND/NEG
Serum	100	100/0/0/0	76/24	76/0/0/0
Plasma	100	100/0/0/0	78/22	78/0/0/0
Total	200	200/0/0/0	154/46	154/0/0/0

Overall, the clinical performance of the Geenius™ HIV 1/2 Supplemental Assay was considered by the committee as appropriate for a supplemental blood donor screening Intended Use.

ii. PMA clinical studies

The results from the clinical studies performed to support PMA BP140120 for the diagnostic intended use of the Geenius™ HIV 1/2 Supplemental Assay have been included in the current submission as additional supporting data for the proposed Intended Use for supplemental blood donor screening.

Clinical specificity

Clinical specificity of the Geenius™ HIV 1/2 Supplemental Assay was evaluated in 240 samples from 120 individuals in a low risk population. Sample matrices tested included serum, EDTA plasma, and heparin plasma. No false positive or invalid results were observed. The indeterminate rate was 2.5% (6/240). Clinical specificity was also evaluated using 100 samples that were false positive (i.e., repeatedly reactive) on an FDA licensed or approved HIV test. None of the 100 samples were positive or invalid on the Geenius™ HIV 1/2 Supplemental assay and the indeterminate rate was 6% (6/100). Specificity statistics are presented on the labeling with descriptive tables because indeterminate samples are considered neither false positive nor negative.

Clinical sensitivity

Clinical sensitivity of the Geenius™ HIV 1/2 Supplemental Assay in serum and plasma (EDTA and lithium heparin) was evaluated using 598 samples prospectively collected from 299 known HIV-1 positive patients. Results are presented in Table 16.

Table 16. Clinical sensitivity in known HIV-1 positive patients in serum and plasma.

Matrix	# tested	Geenius™ POS/IND/ NEG	Geenius™ Sensitivity (95% CI)	Rapid HIV 1/2 Supp. Diff. Assay	HIV-1 Western Blot	FDA licensed HIV-1/HIV-2 EIA
Serum	299	297/2[b]/0	99.33% (97.59-99.82%)	99.00%* (296/299)	99.00%** (296/299)	100% (299/299)
EDTA plasma	151	150/1[c]/0	99.34% (96.34-99.88%)	N/A	N/A	N/A
Heparin plasma	148[a]	147/1[c]/0	99.32% (96.27-99.88%)	N/A	N/A	N/A

[a] Heparin plasma: 150 samples were collected; 2 test results were invalid and 1 was double enrolled and was excluded.

[b] Two (2) HIV-1 patient serum samples were HIV-1 indeterminate on the Geenius™ HIV 1/2 Supplemental Assay.

[c] Of the 2 HIV-1 patient samples that had HIV-1 indeterminate results for serum, 1 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.

* Three (3) samples were indeterminate on the Rapid HIV 1/2 Supplemental Differentiation Assay, including the 2 HIV-1 patient serum samples that were indeterminate on the Geenius™ Supplemental Assay.

**Three (3) samples were indeterminate on the HIV-1 Western blot, including the 2 AIDS patient serum samples that were indeterminate on the Geenius™ HIV-1/2 Supplemental Assay.

The invalid rate for the known HIV-1 positive serum and plasma samples was 0.33% (2/600) and the indeterminate rate was 0.67% (4/598).

Clinical sensitivity of the Geenius™ HIV 1/2 Supplemental Assay was also evaluated using 424 prospectively collected samples from 212 known CDC Stage 3 AIDS patients. Results are presented in Table 17.

Table 17. Clinical sensitivity in known CDC Stage 3 AIDS patients in serum and plasma.

Matrix	# tested	Geenius™ POS/IND/ NEG	Geenius™ Sensitivity (95% CI)	Rapid HIV 1/2 Supp. Diff. Assay	HIV-1 Western Blot	FDA licensed HIV-1/ HIV-2 EIA
Serum	212	210/2[b]/0	99.06% (96.62-99.74%)	98.58%* (209/212)	98.58%* (209/212)	100% (212/212)
EDTA plasma	89	88/1[c]/0	98.88% (93.90-99.80%)	N/A	N/A	N/A
Heparin plasma	123[a]	122/1[c]/0	99.19% (95.53-99.86%)	N/A	N/A	N/A

[a] Heparin plasma: 124 samples were collected, and 1 was double enrolled and was excluded.

[b] Two (2) patient serum samples were HIV-1 indeterminate.

[c] Of the 2 patient samples that had HIV-1 indeterminate results for serum, 1 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.

* Three (3) samples were indeterminate on either the Rapid HIV 1/2 Supplemental Differentiation Assay or the HIV-1 Western Blot, including the two samples that were indeterminate on the Geenius™ Supplemental Assay.

Reactivity of the Geenius™ HIV 1/2 Supplemental Assay for HIV-2 was evaluated using 200 known HIV-2 antibody-positive samples. Of the 200 known HIV-2 antibody positive samples, 38.50% (77/200) were interpreted as only HIV-2 Positive, 54.00% (108/200) were interpreted as HIV-2 with HIV-1 cross reactivity, 6.00% (12/200) were interpreted as HIV Untypable (undifferentiated), 1.50% (3/200) were interpreted as HIV-2 indeterminate. All samples from the known 200 HIV-2 positive subjects were positive on a third generation FDA licensed HIV-1/HIV-2 EIA reference test (historical data).

Reactivity of the Geenius™ HIV 1/2 Supplemental Assay was also assessed for HIV-1 Group M samples, using one hundred thirty-six (136) HIV-1 antibody positive Group M subtype specimens (A, A1, B, C, D, F, F2, G, A/E, A/G, H, J, K, U, CRFs) and 15 known HIV-1 Group O samples. The reactivity of the Geenius™ HIV 1/2 Supplemental Assay for the 136 HIV-1 Group M Subtype samples tested was 99.26% (135/136) HIV-1 Positive, with a 95% CI of 95.95-99.87%. One Group M sample was reported as HIV Positive untypable. 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.

Performance panel clinical testing

The Geenius™ HIV 1/2 Supplemental Assay was evaluated with commercially available HIV performance panels to determine the performance of the test with known HIV-positive specimens with specific characteristics. Testing with HIV performance panels is summarized in Table 18.

Table 18. Performance panel testing results.

Panel(s)	Description	Result with Geenius™ HIV 1/2 Supplemental Assay
HIV-1/HIV-2 Performance Panel	7 HIV-1 positive; 7 HIV-2 positive	7 HIV-1 positive; 5 HIV-2 positive, 1 HIV-2 indeterminate, 1 HIV-2 positive on 2 of 3 lots tested (HIV-2 indeterminate on 3rd)
HIV-1 Incidence/Prevalence Panel	7 new HIV-1 infections; 8 HIV-1 long-standing infections	All 15 HIV-1 positive
HIV Seroconversion Panels	230 samples in 26 panels	71/157 HIV-1 positive compared to 65/157 on Rapid HIV 1/2 Supp/Diff and 56/157 on Western Blot

Clinical Reproducibility

Clinical reproducibility of the Geenius™ HIV 1/2 Supplemental Assay was evaluated using a 17-member reproducibility panel tested at 3 sites (1530 replicates). The panel included 5 members (HIV-1 positive, HIV-1 indeterminate, HIV-2 positive, HIV-2 indeterminate, HIV-negative) each of serum, EDTA plasma and heparin plasma and 2 Geenius™ HIV 1/2 Supplemental Assay kit controls for a total of 17 panel members. Each panel member was tested twice a day (AM and PM), 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). Results are shown in Table 19.

Table 19. Clinical reproducibility results by panel member.

Panel member	Results	% agreement	95% CI
HIV-1 antibody positive serum	90/90 HIV-1 positive	100%	95.91-100%
HIV-1 antibody positive EDTA plasma	89/89 HIV-1 positive	100%	95.86-100%
HIV-1 antibody positive heparin plasma	90/90 HIV-1 positive	100%	95.91-100%
HIV-1 indeterminate serum	85/89 HIV-1 indeterminate	95.51%	89.01-98.24%
HIV-1 indeterminate EDTA plasma	84/87 HIV-1 indeterminate	96.55%	90.35-98.82%
HIV-1 indeterminate heparin plasma	85/90 HIV-1 indeterminate	94.44%	87.65-97.60%
HIV-2 indeterminate serum	80/86 HIV-2 indeterminate	93.02%	85.60-96.76%
HIV-2 indeterminate EDTA plasma	76/88 HIV-2 indeterminate	86.36%	77.66-92.02%
HIV-2 indeterminate heparin plasma	85/89 HIV-2 indeterminate	95.51%	89.01-98.24%
HIV-2 antibody positive serum	90/90 HIV-2 positive	100%	95.91-100%
HIV-2 antibody positive EDTA plasma	88/90 HIV-2 positive	97.78%	92.26-99.39%
HIV-2 antibody positive heparin plasma	89/89 HIV-2 positive	100%	95.86-100%
HIV non-reactive serum	89/90 HIV negative	98.89%	93.97-99.80%
HIV non-reactive EDTA plasma	89/90 HIV negative	98.89%	93.97-99.80%
HIV non-reactive heparin plasma	90/90 HIV negative	100%	95.91-100%
Kit positive control serum	90/90 HIV-1/2 positive	100%	95.91-100%
Kit negative control serum	89/90 HIV negative	98.89%	93.97-99.80%

iii. Clinical Major Review Issues

1. During clinical and statistical review, it was noted that the sponsor had included indeterminate results with negative results in the specificity calculations. This was improper because indeterminate results are neither false positive nor negative. The sponsor was asked to remove the specificity calculation from the report and provide only the descriptive statistics for the specificity study; the specificity calculation did not appear on the draft labeling. In their July 1, 2019 response to the CR letter, the sponsor provided

an updated report with the specificity calculation removed. The issue was considered resolved.

2. The proposed Intended Use currently reads:
   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 serum, or plasma samples (EDTA, lithium heparin, sodium citrate, and CPD) from blood donors.
   The Geenius™ HIV 1/2 Supplemental Assay is intended for use as an additional, more specific test for human serum and plasma samples with repeatedly reactive results by an FDA licensed HIV-1/HIV-2 blood donor screening test. The results of the Geenius™ HIV 1/2 Supplemental Assay are read and interpreted only with the Geenius™ Reader with dedicated software.
   FDA requested that the sponsor modify the wording to clarify that the Geenius HIV 1/2 Supplemental Assay should be used with blood screening devices that test for HIV antibody, rather than any HIV screening test (e.g., nucleic acid tests).

b) BIMO – Clinical/Statistical/Pharmacovigilance

A Bioresearch Monitoring (BIMO) inspection was conducted at one clinical investigator study site that participated in the conduct of Protocol PR.IDD.GBD.02.ARC. The inspection did not reveal significant issues that impact the data submitted in this original BLA.

c) Pediatrics

N/A

d) Other Special Populations

N/A

7. Advisory Committee Meeting

No advisory committee meeting was deemed necessary for this BLA.

8. Other Relevant Regulatory Issues

N/A

9. Labeling

The Advertising and Promotional Labeling Branch (APLB) found the proposed Instructions for Use (IFU), and the package and container labeling, acceptable from a promotional and comprehension perspective.

10. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The Review Committee reviewed the original submission, resubmission and related Amendments. All review issues have been resolved; therefore, the Review Committee recommends licensure of the Geenius™ HIV 1 /2 Supplemental Assay.

b) Risk/ Benefit Assessment

The benefit/risk analysis demonstrates that the benefit of the Geenius™ HIV 1 /2 Supplemental Assay outweighs any risk to the blood donor and the safety of the nation's blood supply. The clinical studies demonstrate a sensitivity of 100% (95% CI of 98.12–100%) in known HIV-1 positive specimens, indicating a low probability of a false negative result. Among 200 normal blood donors and 100 HIV false-positive blood donors (unconfirmed repeat reactive on HIV EIA) tested with the Geenius™ HIV 1/2 Supplemental Assay in clinical trials, the false positive rate of 0% for both populations and indeterminate rate of 4.0% in EIA false positives suggests a low probability of a false positive result.

c) Recommendation for Postmarketing Activities

No postmarketing activities have been proposed for this application.