Summary Basis for Regulatory Action

Date: December 9, 2014

From: Pradip N. Akolkar, Ph.D., Scientific Lead, BLA Review Committee

BLA/ STN#: 125475/0

Applicant Name: MP Biomedicals Asia Pacific Pte. Ltd.

Date of Submission: March 4, 2013

Complete Response letter: December 12, 2013

Response to CR letter received: June 13, 2014

MDUFMA Goal Date: December 13, 2014

Trade Name: MP Diagnostics HTLV Blot 2.4

Proper Name: Human T-Lymphotropic Virus Types I & II

Indication: Detection of antibodies to HTLV-I (anti-HTLV-I) and/or antibodies to HTLV-II (anti-HTLV-II) in human serum and plasma specimens.

Recommended Action: Approval

Offices Signatory Authority: Jay S. Epstein, M.D.
Director, OBRR /CBER

Signatory Authorities Action:

- □ **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.**

Offices Signatory Authority: Mary Malarkey
Director, OCBQ /CBER

Signatory Authorities Action:

- □ **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.**

Material Reviewed/Consulted - List of Specific documentation used in developing the SBRA

Clinical Review	Pradip Akolkar, Subhash Dhawan
Preclinical Review	Krishnakumar Devadas
Statistical Review	Paul Hshieh
CMC Review/ Facilities	Krishnakumar Devadas, Richard Coats, Jennifer Schmidt
Establishment Inspection Report	Pradip Akolkar, Kimberly Lewnadowski-Walker, Babatunde D. Babalola
Lot Release Review	Leslyn Aaron, Kori Francis, Stephen Kerby, Susan Zullo
Software and Instrumentation	Hilary Hoffman
BIMO	Erin Mcdowell
Labeling and Promotion	Dana Martin
OCTGT Review	Karoll Cortez
Regulatory Project Manager	Cherie Ward-Peralta, Thomas J. Maruna

I. Introduction

MP Biomedicals Asia Pacific Pte. Ltd., a company of MP Biomedicals, LLC, Santa Ana, California, submitted a Biologics License Application (BLA) for the licensure of the MP Diagnostics™ HTLV Blot 2.4, which is manufactured by MP Biomedicals.

Intended Use

The MP Diagnostics HTLV Blot 2.4 is a qualitative enzyme immunoassay intended for confirming the presence of and differentiating antibodies to HTLV-I and HTLV-II in human serum and plasma. It is intended for use as a supplemental (additional, more specific) test for human serum and plasma specimens with repeatedly reactive results by an FDA licensed HTLV-I/II donor screening test. The MP Diagnostics HTLV Blot 2.4 is intended for use in a manual mode or a semi-automated mode using the MP Diagnostics AutoBlot System 20. This test is not intended for use in medical diagnosis.

II. Background

A. Description of HTLV-I and HTLV-II

Human T-cell Lymphotropic Viruses (HTLVs) are pathogenic retroviruses that may cause severe hematological and neurological diseases in infected individuals. The HTLV family contains two well-studied members, HTLV-I and HTLV-II. HTLV-I is known as the etiological agent of adult T-cell leukemia/lymphoma (ATL), HTLV-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP), and HTLV-associated uveitis. HTLV-II is genetically (70% nucleotide identity) and immunologically related to HTLV-I. It was first isolated from a patient with an unusual form of hairy T-cell leukemia. However, its causative role in disease development has not been established. Both viruses can be transmitted through contaminated blood products

B. HTLV Testing of Blood Donors

Blood donor testing for HTLV-I and HTLV-II infections is performed with licensed immunoassays that detect virus specific antibodies in serum/plasma using immunoassays. As with all screening immunoassays, supplemental tests such as Western Blot (WB) are needed for additional testing of repeatedly reactive (RR) specimens to confirm true positive screening test results indicative of the infections and to identify false positive screening test results. In the case of HTLV-I/II, such supplemental serological tests must be capable of identifying antibodies to core (*gag*) and envelope (*env*) proteins of HTLV-I/II to ascertain that the reactivity seen in the screening assay is due to the presence of infection and not due to non-specific cross-reactivity of human antibodies to other proteins. Historically, several WB assays that were developed using whole viral lysate antigens had very low levels of *env* proteins and were difficult to interpret due to the low reactivity of specimens to poorly represented *env* proteins. An important advance in HTLV serology has been the development of recombinant proteins and identification of immunodominant peptides. The use of WBs and line immunoblots incorporating recombinant viral proteins and immunodominant peptides has improved the sensitivity of serological assays for the detection of antibodies to HTLV-I/II.

Currently all donations of blood and blood components for transfusion are required to be screened for evidence of infection with HTLV-I and HTLV-II (21 CFR 610.40(a)(5) and (6)). FDA has licensed combination HTLV-I/II tests to screen donors of transfusible blood products. Antibodies to HTLV-II often are cross-reactive with HTLV-I antigens, and currently licensed screening tests are unable to distinguish between antibodies to HTLV-I and HTLV-II.

Currently, there is no FDA-licensed supplemental test to confirm RR results on an HTLV-I/II antibody screening test on a donor's sample. If a donation tests RR on an HTLV-I/II antibody screening test, the unit is not used for transfusion. The donor is deferred from donating if a donation tests RR with two different licensed screening tests or with the same licensed screening test on two different donations. Supplemental serological tests for HTLV-I/II are needed to identify false positive results or to confirm a RR HTLV antibody screening test result, and also to differentiate HTLV-I and HTLV-II seropositive specimens so that donors can be adequately counseled in regard to their need for follow-up testing and possible medical evaluation. A supplemental test must be performed on each donation found to be reactive by a screening test for HTLV-I and HTLV-II whenever a supplemental test has been approved for such use by FDA (21 CFR 610.40(e)). Supplemental testing is also needed for possible donor requalification/reentry. Studies by blood establishments indicate that in the absence of HTLV supplemental assays there is a significant donor loss due to deferral of non-infectious donors whose donations are repeatedly reactive on a screening test.

C. PHS recommendations for HTLV Western Blot Interpretation

The criteria for HTLV-I/II Western blot positivity were adopted by a U.S. Public Health Service working group in 1988[1], and modified in 1993[2]. The current PHS recommended criteria for HTLV blot positivity are as follows: To be considered as seropositive in the U.S., a specimen that is RR on a screening test for antibodies to HTLV-I/II should demonstrate immunoreactivity to both a *gag* gene product (i.e., p19 and/or p24) and to an *env* gene product (gp46 and/or gp61/68) on the additional test (e.g., WB). With development of HTLV blots incorporating a recombinant transmembrane *env* protein, p21e, reactivity to p21e along with reactivity to *gag* protein(s) and *env* gp46 is required for a specimen to be considered positive for antibodies to HTLV-I/II. The relative intensity of reactivity with *gag* proteins p19 and p24 on WB based on HTLV-I antigens can be used to differentiate HTLV-I from HTLV-II. For specimens with antibodies to HTLV-I, the intensity for p19 is equal to or greater than for p24, and for specimens with antibodies to HTLV-II the intensity for p24 is greater than for p19.

Reactive serum or plasma specimens that do not satisfy these criteria for positivity, but that do show immunoreactivity to at least one HTLV gene product (e.g., *gag* or *env*) are designated as indeterminate.

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[1] Center for Disease Control and prevention (CDC). Current trends: Licensure of screening tests for antibody to human T-lymphotropic virus type I. MMWR 1988; 37:736–740,745–747.

[2] Center for Disease Control and prevention (CDC). Recommendations for counseling persons infected with human T-lymphotropic virus, type I and II. MMWR.1993; 42 (RR-9):1-13.

Serum or plasma specimens with no immunoreactivity to any HTLV gene products on an additional, more specific test (e.g., WB) are considered to have been false positives on the screening test.

D. California Department of Public Health Laboratory Testing Algorithm

In the absence of an FDA licensed supplemental test to confirm the RR results of an HTLV-I/II screening assay, information from a laboratory-developed testing algorithm (California Department of Public Health Laboratory (CDPHL) is currently used voluntarily by blood establishments for counseling individuals who have RR results using an HTLV-I/II screening test. The CDPHL Algorithm consists of a series of laboratory developed tests (LDTs), including an enzyme-linked immunosorbent assay (ELISA), an indirect fluorescent antibody assay (IFA), a WB, and a radioimmunoprecipitation assay (RIPA). The tests are run in a defined sequence.

Specimens that are RR on licensed HTLV-I/II screening test are tested with assays developed by CDPHL. The specimens are run first on ELISA; if RR on ELISA, they are then tested with IFA. IFA-negative specimens are tested using a CDPHL WB, and specimens with positive or indeterminate results on WB are tested with RIPA. IFA positive specimens are titrated for reactivity to HTLV-I or HTLV-II for differentiation. IFA inconclusive specimens are tested by WB and RIPA. The overall interpretation is determined by the results of all tests performed.

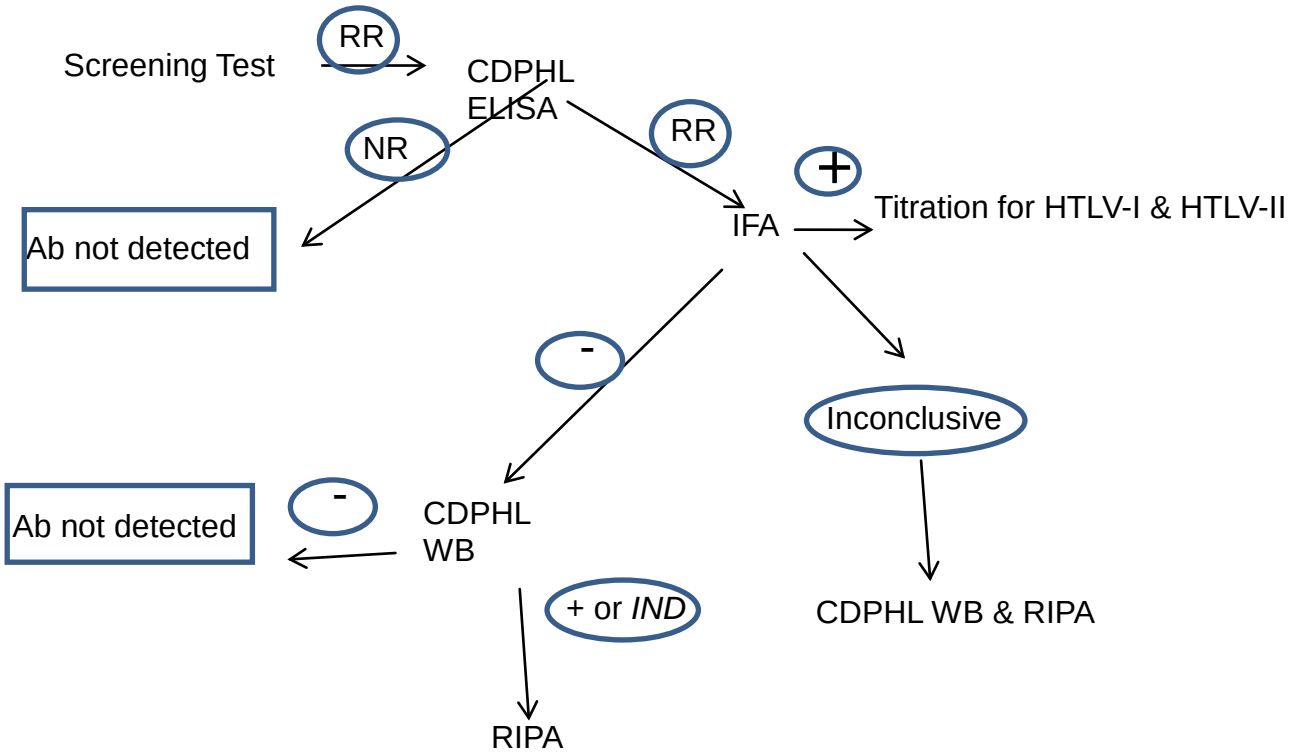
Upon receipt at CDPHL, all specimens are tested using the in-house HTLV ELISA. Specimens that test non-reactive on the CDPHL ELISA are not subjected to any further testing and are reported as HTLV antibody not detected.

Specimens that are RR on the CDPHL HTLV ELISA, defined as two out of three tests above the assay cut-off value, are subjected to further testing by an HTLV IFA. If the HTLV IFA is reactive to both HTLV-I and HTLV-II antigens, the sample is confirmed as positive for antibodies to HTLV and further typed using IFA relative endpoint titration to determine if the sample is positive for HTLV-I or HTLV-II. The sample is then reported as antibody detected with the HTLV sub-type differentiated. According to the CDPHL algorithm, specimens that are positive but cannot be differentiated between HTLV-I and –II are considered inconclusive. Specimens that are inconclusive or non-reactive on IFA proceed to CDPHL WB testing.

The CDPHL WB is an enzyme immunoassay that utilizes a combination of native proteins derived from an HTLV-I viral lysate along with a recombinant p21e antigen. The interpretation of the CDPHL WB is based on the presence or absence of seven bands: p19; p24; p28; p36; gp46; p53; and p21e. A positive sample on the CDPHL HTLV WB will show the presence of the p19 and/or p24 bands, plus p21e. Specimens are indeterminate if only p21e banding is present, and negative if p21e is absent regardless of core bands p19 and/or p24. If two of the test results are concordant (IFA inconclusive/WB positive or IFA negative/WB negative), results will be reported out as the overall interpretation (i.e., antibody detected or not detected); specimens with discordant IFA and WB results will be tested using an in-house RIPA.

The in-house RIPA for HTLV-I and HTLV-II is performed in cases where the sample IFA and WB results are discordant.

Flow of testing in the CDPHL Algorithm:



Since there is no licensed supplemental test for HTLV-I/II RR specimens, the CDPHL Algorithm for HTLV was used as a comparator in the studies conducted to evaluate the performance of the MP Diagnostics HTLV Blot 2.4. The CDPHL Algorithm was validated using a well characterized panel (PCR positive) of specimens from HTLV-I and HTLV-II infected individuals (J. Diggs, November 1, 2013 BPAC presentation).

E. Description of the MP Diagnostics HTLV Blot 2.4

The MP Diagnostics HTLV Blot 2.4 is intended as a supplemental test for RR blood donor specimens to confirm the presence of anti-HTLV-I/II antibodies and to differentiate between HTLV type-I and HTLV type-II infections for donor notification and counseling. The possible serological profiles defined by the HTLV Blot 2.4 include the following: HTLV-I Seropositive, HTLV-II Seropositive, HTLV-I/II Seropositive, Seronegative, and Indeterminate.

The MP Diagnostics HTLV Blot 2.4 uses a combination of HTLV-I/II genetically engineered proteins (i.e., recombinant antigens) and HTLV-I viral proteins derived from native, inactivated viral particles (i.e., viral lysate). The differentiation between HTLV-I and HTLV-II is accomplished through the use of rgp46-I, a unique HTLV-I envelope recombinant protein, and rgp46-II, a unique HTLV-II envelope recombinant protein. Both proteins are derived from the central region of the external glycoprotein, gp46, of the respective HTLV-I and HTLV-II viruses. GD21, representing a common yet specific HTLV-I and HTLV-II antigen, is an envelope recombinant protein derived from a truncated region of p21e (rgp21) that is also used to enhance

the specificity of envelope antibody detection. GD21 has demonstrated greater specificity for HTLV-I/II than p21e, an earlier version of the recombinant antigen. The antigenicity exhibited by these recombinant proteins is either common to HTLV-I and HTLV-II antibodies or type specific to one of the two viral types to allow confirmation and discrimination in a single assay.

III. Principle of the Test

HTLV-I viral proteins, derived from native, inactivated viral particles (viral lysate) and added recombinant protein GD21are --------(b)(4)-----transferred to nitrocellulose membranes by ----------------(b)(4)---- Recombinant glycoprotein gp46 for HTLV-I (rgp46-I or MTA-1), gp46 for HTLV-II (rgp46-II or K55) and an anti-human IgG to serve as a sample addition control are ----------(b)(4)----------. Individual nitrocellulose strips are incubated with diluted serum or plasma specimens; specific antibodies to HTLV-I/II, if present in the specimen, will bind to the HTLV-I/II proteins on the strip. The strips are washed to remove unbound materials, and the remaining antibodies, bound to the HTLV proteins on the strips, are visualized using a series of reactions with goat anti-human IgG conjugated with alkaline phosphatase and the substrate, BCIP/NBT.

Of the proteins applied to the nitrocellulose strips, five are used to confirm the presence of antibodies against HTLV-I/II. These are the following: rgp46-I, rgp46-II, GD21, p19, and p24.

Type-specific recombinant envelope protein rgp46-I is specific for HTLV-I, while rgp46-II is specific for HTLV-II; these antigens are used to differentiate between HTLV-I and HTLV-II infections. However, reactivity against both of these antigens may be present in some positive specimens, precluding virus differentiation.

Two HTLV-I *gag* proteins, p19 and p24, which are reactive with antibodies to HTLV-I and are cross-reactive with antibodies to HTLV-II, are used to confirm the presence of antibodies. Differentiation between the HTLV viral types is possible based the relative intensity of antibody reactions with the native HTLV-I *gag* proteins p19 and p24. If the intensity of the p19 band is greater than or equal to that of the p24 band, HTLV-I infection is indicated, and if the intensity of p24 is greater than that of p19, HTLV-II infection is indicated.

GD21, a third recombinant envelope protein, is broadly immunoreactive with sera or plasma from HTLV-I and HTLV-II infected individuals and should be recognized by antibodies in all positive specimens.

IV. Chemistry, Manufacturing and Controls (CMC)

The viral lysate used in the manufacture of the MP Diagnostics HTLV Blot 2.4 is prepared from virus grown in HuT 102 cells that has been purified by ultracentrifugation on a sucrose gradient ----------(b)(4)----------. As a result, the presence of non-viral bands is greatly minimized, making it easier for operators to read the results. In addition, due to use of purified virus, the blot does not have the *env*

precursor gp61/68 protein band. In addition to purified HTLV-I viral lysate, the following HTLV antigens are utilized in the manufacture of the MP Diagnostics HTLV Blot 2.4 strips:

- A recombinant *env* protein, GD21, that is a portion of the HTLV-I p21e protein and is specific for both HTLV-I and HTLV-II;
- An HTLV-I specific recombinant *env* protein, rgp46-I (MTA-1);
- An HTLV-II specific recombinant *env* protein, rgp46-II (K55);

In order to help the users to identify the bands correctly, MP Biomedicals has included a Lot-Specific Protein Finder (Fig. 1). The Protein Finder will help the user to identify the major bands and distinguish them from all of the minor bands that are inherent to the proteins of the HTLV-I virus lysate. On the Protein Finder shown in Fig. 1, the sample strip (which comes from the same lot of strips provided in the kit) is for an HTLV-I positive sample. The arrows to the right of Fig. 1 indicate the bands that are of diagnostic significance in the Positive interpretation of the WB result. An Intensity Finder (Fig. 2) is provided as an aid to determine visually the relative intensity of the bands on each blot for differentiation between HTLV-I and HTLV-II. Major band intensities are scored against those on the Intensity Finder to provide their interpretation. However, this determination is not a quantitative or semi-quantitative measure. Although the actual intensity of the bands may be different between labs/users, the relative intensity will remain the same for a given specimen.

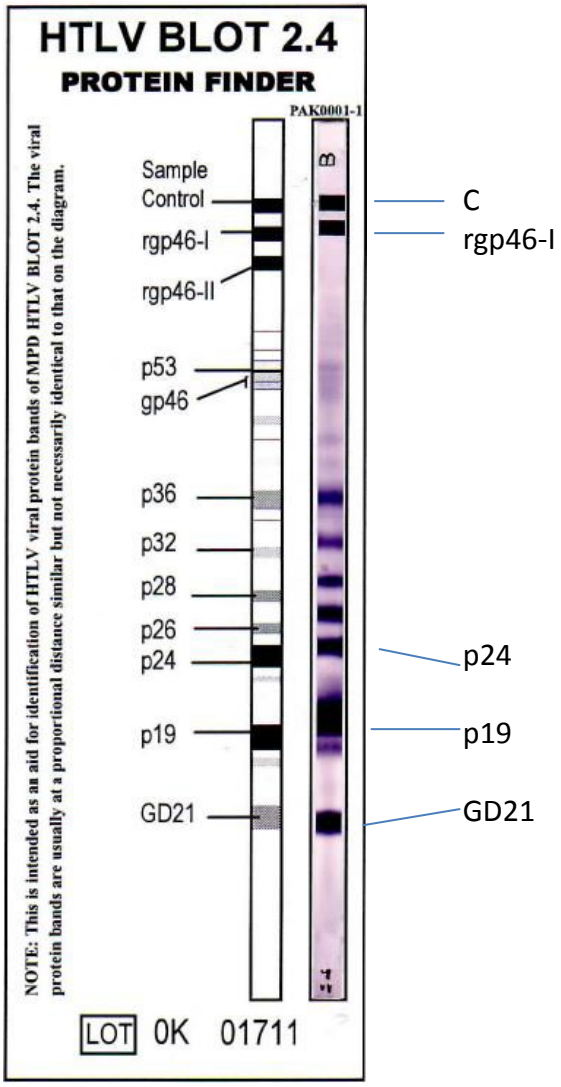
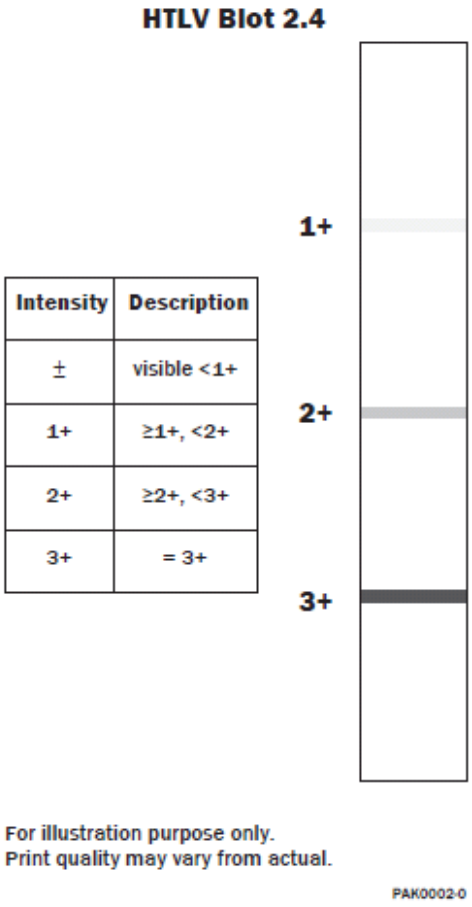


Fig. 1: Lot-Specific Protein Finder



Intensity	Description
±	visible <1+
1+	≥1+, <2+
2+	≥2+, <3+
3+	= 3+

Fig. 2: Intensity Finder

HTLV Blot 2.4 Interpretation Criteria	
Negative	• No reactivity to HTLV specific proteins; or • Any combination of *gag* proteins excluding p24 (i.e. p19, p26, p28, p32, p36, p53 ["HTLV *gag* Indeterminate Pattern," or "*HGIP*"]); or • Any single *gag* protein other than isolated p19 or p24 (i.e., p26, p28, p32, p36, or p53 only)
HTLV-I Positive	• Reactivity to p19, GD21, ***and*** rgp46-I: or • Reactivity to p19, p24, ***and*** GD21, with reactivity to p19 greater than or equal to p24
HTLV-II Positive	• Reactivity to p24, GD21, ***and*** rgp46-II: or • Reactivity to p19, p24, ***and*** GD21, with reactivity to p24 greater than p19
HTLV-I/II Positive Undifferentiated	• Reactivity to p19, p24, GD21, rgp46-I, ***and*** rgp46-II
Indeterminate	• Reactivity to HTLV specific bands that do not meet the criteria for HTLV-I Positive, HTLV-II Positive, HTLV-I/II Positive, or Negative • Single *gag* protein p24 • Single *gag* protein p19

a. Components of the MP Diagnostics HTLV Blot 2.4 Kit

Component Description	**Quantity Provided**
NITROCELLULOSE STRIPS Incorporated with HTLV-I viral lysate, HTLV-I and II recombinant envelope antigens, and a sample addition control (anti-human IgG) band. Keep dry and away from light.	Available in 18 or 36 strips
NON-REACTIVE CONTROL Inactivated normal human serum, non-reactive for anti-HCV, anti-HIV-1/2, anti-HTLV-I/II and HBsAg. Contains sodium azide and thimerosal as preservatives.	1 vial (80 µL)
STRONG REACTIVE CONTROL I Inactivated human serum with high titer antibodies to HTLV-I and non-reactive for anti-HCV, anti-HIV-1/2 and HBsAg. Contains sodium azide and thimerosal as preservatives.	1 vial (80 µL)
	1 vial

Component Description	Quantity Provided
STRONG REACTIVE CONTROL II Inactivated human serum with high titer antibodies to HTLV-II and non-reactive for anti-HCV, anti-HIV-1/2 and HBsAg. Contains sodium azide and thimerosal as preservatives.	(80 µL)
LYOPHILIZED STOCK BUFFER To be reconstituted in reagent grade water. Tris buffer with heat inactivated animal and non-animal proteins. Contains thimerosal as preservative.	1 or 2 bottles (each to be reconstituted to 100 mL)
WASH BUFFER CONCENTRATE (20X) Tris with Tween-20. Contains thimerosal as preservative.	1 bottle (70 mL)
CONJUGATE Goat anti-human IgG conjugated with alkaline phosphatase. Contains sodium azide as preservative.	1 vial (120 µL)
SUBSTRATE Solution of 5-bromo-4-chloro-3-indolyl-phosphate (BCIP) and nitroblue tetrazolium (NBT).	1 bottle (100 mL)
BLOTTING POWDER Non-fat dry milk	10 packets (1 g each)
Instructions for Use (IFU)	1 copy
Lot-Specific Protein Finder	1 piece
Intensity Finder	1 piece
Forceps	1 pair
Disposable 9-well incubation tray (manual use only and packed separately from the kit)	2 or 4 trays
HTLV Blot 2.4 Report Sheet	1 piece

b. Stability

Real-time Stability testing for the HTLV Blot 2.4 kit and kit components was performed through an (b)(4) month testing time point using an FDA approved stability study protocol. Kits were stored at the recommended storage temperature of 2-8° C. Testing is scheduled to be carried out for a total of (b)(4) months at three months intervals.

Based on the data submitted, stability / expiration dating for the kit will be 15 months at the recommended storage temperature of 2-8^{o}C. MP Biomedicals will be continuing the real time

stability testing of the HTLV Blot 2.4 kits up to (b)(4) months at 3 month interval as per the stability study protocol approved during the review of the BLA.

c. Manufacturing Quality Control

The MP Diagnostics HTLV Blot 2.4 kits are manufactured at MP Biomedicals Asia Pacific Pte. Ltd. facility in Singapore.

Raw materials intended for manufacturing and for use in the assay components are subject to appropriate quality control evaluations before they are accepted for use in manufacturing. The quality of the kit components is assessed at multiple stages during manufacture using tests to ensure conformance to acceptable specifications. Acceptance criteria and specifications have been established for all kit components.

Production of test kit components is monitored by in-process testing. Product purity and potency are assured through evaluation of multiple parameters including product appearance, bioburden, and performance testing. Assay performance of test kits is assessed through laboratory evaluations using an in-house panel of specimens containing HTLV-I positive, HTLV-II positive, and negative specimens. In addition, each kit lot is also evaluated in-house using CBER Lot Release Panels, and the test is run both in manual and in semi-automated mode.

d. CBER Lot Release

Each new lot of a licensed retroviral test kit is subject to lot release including testing at the Center for Biologics Evaluation and Research (CBER) using panels developed for that purpose.

Three conformance lots of MP Diagnostics HTLV Blot 2.4 were received and tested in the Division of Biological Standards and Quality Control (DBSQC). CBER Reference Panels (CBER HTLV-I Reference Panel 18 and CBER HTLV-II Reference Panel 15) were used to evaluate kit function. All three lots demonstrated the expected reactivity on the CBER Reference Panels. The following is a list of the lots submitted in support of approval:

Lot Number	Expiration Date	Lot Release Determination
AK3018	05/01/2015	Pass
AK3019	05/01/2015	Pass
AK4005	05/01/2015	Pass

MP Diagnostics HTLV Blot 2.4 will be the first FDA licensed supplemental test for confirmation and differentiation of antibodies to HTLV-I and HTLV-II for donor specimens that are repeatedly reactive on an FDA licensed donor screening test. Therefore DBSQC agrees that from a safety perspective, the best method to assure acceptable product performance is ongoing lot release testing.

e. Instrument and Software

Instrument:
MP Diagnostics AutoBlot System 20: The MP Diagnostics AutoBlot System 20 is intended as a semi-automatic instrument designed to automate the major portions of the MP Diagnostics HTLV Blot 2.4 assay. The AutoBlot is a closed system designed for use with the MP Diagnostics HTLV Blot 2.4 only. The AutoBlot is a firmware controlled device that automates the processing steps of the HTLV Blot 2.4. The processing steps performed include dispensing and aspiration of reagents and incubation of the nitrocellulose strips after sample application. The AutoBlot does not process specimens nor does it read or interpret results.

Software:
The MP Diagnostics AutoBlot System 20 is automated by firmware that controls the dispensing/aspirating arm. The customized MP Diagnostics HTLV Blot 2.4 assay is preprogrammed into the AutoBlot. The AutoBlot software device has been established as a Major Level of Concern due to its intended use in combination with a biologic (donor screening assay). The AutoBlot is operated by firmware version 2.64 and is programmed with the HTLV Blot 2.4 assay only. The firmware automates the addition of reagents as well as notifies the operator to manually add the nitrocellulose strips and specimens and controls.

The Software Requirements Specifications, Software Design Specification, Traceability Matrix, Software Development Life Cycle Plan, and verification/validation protocols and results were reviewed by CBER and found to be adequate.

f. Facilities Review/Pre-License Inspections

The facilities involved in the manufacture of the HTLV Blot 2.4 are listed in the table below. The activities performed and the inspectional history of the facilities is included in the table. Summaries of inspections are presented after the table.

Table of the Manufacturing Facilities for HTLV Blot 2.4

Organization / Site	**Responsibility**	**FEI Number**	**Inspection Date**
MP Biomedicals Asia Pacific Pte. Ltd. 2, Pioneer Place Singapore 627885	Manufacture of GD21, MTA-1 and K55 recombinant antigens. Specification developer for all of the *in vitro* substances as well as for the manual *in vitro* product. Cell culture, protein purification, quality control testing, manufacture of components for blot kit, component labeling and kit assembly.	3008819649	8/19-22/2013 Pre-License Inspection performed by ORA and CBER Decision: VAI

Organization / Site	Responsibility	FEI Number	Inspection Date
MP Biomedicals Solon, OH	QC release testing verifies the semi-automated version of the HTLV Blot with their instrument system. HTLV Blot incoming QC activities. Specification developer for the AutoBlot System 20 as well as for the automated HTLV Blot 2.4. Distribution of final test kit.	DRN# 2419955	Inspection was waived based on the acceptable FDA compliance history.
----------. ---------(b)(4)-------- ------- ---------- ---------	---------- ----------(b)(4)---------- ----------. ---------- --------(b)(4)---------- --------	-------(b)(4)--------	-----(b)(4)---- Pre-License Inspection performed by ORA at CBER request Decision: VAI

All inspections performed were classified as Voluntary Action Indicated (VAI). Responses by the companies to issued FDA Form 483 observations have been submitted, reviewed, and found acceptable. One inspection was waived based on the facility not being involved in the manufacture of the manual HTLV Blot 2.4 kit. Summaries of the inspections performed in support of this submission and the inspection waiver follow.

The MP Biomedicals Asia Pacific Pte. Ltd., 2 Pioneer Place, Singapore 627885 location was inspected from: 8/19/2013 through 8/22/2013.
This pre-license inspection of MP Biomedicals Asia Pacific Pte. Ltd. was conducted by CBER and ORA in support of this application. This was the initial FDA inspection of this firm.

A one-item FDA 483 was issued regarding failure to investigate or take corrective action regarding an out-of specification microbial measurement in one of the laminar flow hoods used in the reagent production area. The firm responded to the 483, the response was reviewed and found to be acceptable.

The pre-license inspection for the MP Biomedicals Solon, Ohio facility was waived.
The MP Biomedicals Solon, Ohio facility is not involved in manufacture of components or release testing of the manual HTLV blot kit. This facility performs release testing of the HTLV Blot 2.4 with the AutoBlot System 20. This activity is similar to testing performed for other Class I and Class II IVD kits manufactured by the firm. The IVD test types manufactured include ----------(b)(4)---------- tests. Based on the information provided in the BLA, the previous inspection report supporting the overall compliance status of the facility and the compliance check of the facility, the Review Committee recommended waiving the pre-approval inspection for the Solon, Ohio facility associated with this BLA.

----------(b)(4)---------- location was inspected ----------(b)(4)----------.
This Pre-license inspection of the instrument manufacturing facility was conducted by ORA per CBER assignment.

A Level II Baseline Inspection which covered all four subsystems (Management Controls, Design Controls, CAPA, Production and Process Controls) was performed to determine the firm's capability to manufacture the AutoBlot System 20 product. In addition, a review of the firm's Medical Device Reporting system was conducted.

An FDA 483, Inspectional Observations, was issued noting the following objectionable conditions: quality audits have not been performed, procedures for design change have not been established, procedures for management review have not been adequately established, and written MDR procedures have not been developed and implemented. The firm provided responses to these observations and the responses were reviewed and found acceptable.

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable.

g. Environmental Assessment

MP Biomedicals requested a categorical exclusion to omit preparation of an environmental assessment, under 21 CFR Part 25.31(c). This request was found acceptable and a categorical exclusion under 21 CFR § 25.31(c) memorandum was approved on November 4, 2013.

V. Performance Characteristics of the MP Diagnostics HTLV Blot 2.4

A. Reproducibility

A reproducibility study performed by the operators trained during the clinical studies was carried out using a panel consisting of one HTLV-I antibody specimen, one HTLV-II antibody specimen, and one HTLV-I/II negative specimen. Each panel member was assayed in duplicate using three lots of MP Diagnostics HTLV Blot 2.4 by three operators at each of the three sites for a total of 54 strips per panel member. In this study, none of the 162 strips (including 54 HTLV-I positives and 54 HTLV-II positives) was incorrectly identified. These data demonstrated that the assay is reproducible across multiple replicates, operators, sites, and kit lots.

B. Specificity

A total of 200 repository specimens from a normal blood donor population were evaluated at three geographically distinct clinical testing sites. These specimens were from blood donors that had previously tested anti-HTLV non-reactive using a licensed HTLV antibody screening assay. The results obtained using the MP Diagnostics HTLV Blot 2.4 were compared with results obtained from matched plasma specimens tested using the CDPHL Algorithm (see Table 1).

Table 1: MP Diagnostics HTLV Blot 2.4 and CDPHL Algorithm Results for HTLV Screening Assay Negative Blood Donor Specimens

MP HTLV Blot 2.4	CDPHL Algorithm			
	Positive	**Indeterminate**	**Negative**	**Total**
Positive	0	0	0	0 (0%)
Indeterminate	0	0	43[a]	43 (21.5%)
Negative	0	0	157	157 (78.5%)
Total	0 (0%)	0 (0%)	200 (100%)	200

[a] There were four specimens with p19 only and eight with p24 only MP Diagnostics HTLV Blot 2.4 results.

The MP Diagnostics HTLV Blot 2.4 identified 157 specimens as Negative and 43 as Indeterminate; there were no specimens identified as Positive in this population. All of these 200 specimens tested Negative by the CDPHL Algorithm; however, 15 were repeatedly reactive by ELISA in the CDPHL Algorithm. Thirteen of these repeatedly reactive specimens were resolved as Negative in the CDPHL Algorithm based on non-reactivity on both the IFA and WB. Two of these 15 specimens, however, showed reactivity with the p21e protein on the WB and were subjected to additional testing using RIPA. A non-reactive result on the RIPA for these 2 specimens resulted in an overall interpretation of Negative by the CDPHL Algorithm. All but one of these 15 specimens was Negative by the MP Diagnostics HTLV Blot 2.4 assay.

There were four specimens with p19 only and eight with p24 only MP Diagnostics HTLV Blot 2.4 results that were interpreted as Indeterminate. In the future, samples with p19 only and p24 only may be reclassified as Negative based on additional studies confirming that interpretation for like samples. It is noteworthy that in the CDPHL Algorithm, Western blots with p19 and p24 only are interpreted as negative.

This study demonstrated a high rate of indeterminacy (21.5%) on ELISA negative specimens for the MP Diagnostics HTLV Blot 2.4. However, there were no false positive test results. **(Note: Specimens that are non-reactive on an FDA licensed HTLV-I/II screening test would not normally be tested using the MP Diagnostics HTLV Blot 2.4, a supplemental assay.)**

Effect of Potentially Interfering Substances

A total of 120 specimens with potentially interfering substances were obtained from well characterized repositories and tested for non-specific reactivity and interference with the HTLV Blot 2.4. Specimen types consisted of the following: elevated bilirubin (n = 20); elevated triglycerides (n = 20); bacterially contaminated specimens (n = 20); hemolyzed specimens (n = 20); icteric specimens (n = 20); lipemic specimens (n = 20). The impact of different potentially interfering substances on the performance of the MP Diagnostics HTLV Blot 2.4 was assessed using the six (6) different groups of specimens as both unspiked specimens and specimens spiked with an anti-HTLV-I or anti-HTLV-II positive plasma specimen to a low level of reactivity at a dilution of 1:80. The results are presented in Table 2.

Table 2: Effect of Potentially Interfering Substances

Potentially Interfering Substance	Level of Potential Interferent	Number of Specimens Tested	Number of Specimens Positive in Unspiked Populations[a]	Number of Specimens Negative in Spiked Populations
Elevated Bilirubin	25.1 to 44 mg/dL	20	0	0
Elevated Triglycerides	859 to 1883 mg/dL	20	0	0
Bacterial Contamination	As determined by gram stain	20	0	0
Hemoglobin	25 to 200 mg/dL	20	1	0
Icteric	Bilirubin > 20 mg/dL	20	0	0
Lipemic	Triglycerides > 400 mg/dL	20	0	0

[a] The following specimens gave Indeterminate results due to high background: one with bacterial contamination, one with high hemoglobin, four icteric, and one lipemic.

Of the 120 specimens, one hemolyzed sample had a false positive result; therefore, a warning statement was added to the package insert for the test that states that specimens with elevated hemoglobin levels may produce erroneous results due to non-specific reactivity. In addition, a high background level on the strip obscured the reading of bands in seven of the 120 specimens (5.8%), giving Indeterminate results. As both spiked and unspiked specimens were affected, it was determined that the higher background was most likely due to the presence of the different interferents.

Potentially interfering substances in anti-HTLV-positive specimens did not impact the sensitivity of the HTLV Blot 2.4 based on absence of false negative test results for spiked specimens. However, indeterminate results were obtained on some specimens due to interference from high background.

Effect of Unrelated Medical Conditions

The effect of potentially interfering medical conditions on the performance of the HTLV Blot was evaluated using 200 specimens from individuals with various medical conditions, including HIV (n = 20), HCV (n = 20), HBV (n = 20), EBV (n = 20), CMV (n = 20), patients vaccinated with the influenza vaccine (n = 10), hemophiliacs (n = 20), dialysis patients (n = 20), multiparous women (n = 10), high rheumatoid factor (n = 20), Hashimoto's disease (n = 10), and Sjogren's disease (n = 10). Specimens were tested both unspiked and spiked with an anti-HTLV-I or anti-HTLV-II positive plasma specimen. The results are shown in Table 3.

Table 3: Effect of Unrelated Medical Conditions

Potentially Interfering Medical Condition	Number of Specimens Tested	Number of Specimens Positive in Unspiked Populations	Number of Specimens Negative in Spiked Populations
HIV	20	1	0
HCV	20	0	0
HBV	20	0	0
EBV	20	0	0[b]
CMV	20	0	0
Influenza Vaccine	10	0	0
Hemophilia	20	1	0
Dialysis	19[a]	0	0
Multiparous Women	10	0	0
Elevated Rheumatoid Factor	20	0	0
Hashimoto's disease	10	0	0
Sjogren's disease	10	1	0

[a] One specimen from the dialysis group was determined to be a true positive based on subsequent testing and was excluded from the analysis.
[b] One spiked specimen from the EBV group tested as Indeterminate instead of Positive.

Of the 200 unspiked specimens, four gave Positive results: one each from the HIV, hemophilia, dialysis, and Sjogren's populations. However, the Positive specimen from the dialysis population was determined to be a true positive based on subsequent testing and was removed from the analysis. Of the 200 spiked specimens, all but one remained Positive: one sample from the EBV population was Indeterminate.

Comparison of Manual vs. MP Diagnostics AutoBlot System 20

The MP Diagnostics HTLV Blot 2.4 assay can be performed manually and in a semiautomated mode using MP Diagnostics AutoBlot System 20. The AutoBlot performs all the incubation and washings of the blot in automatic mode and the results are read and interpreted manually. As part of non-clinical studies 430 specimens were tested using both manual as well as semiautomated mode demonstrating the equivalent performance.

In addition, MP Biomedicals performs routinely lot release testing using both manual and semiautomated methods. The data for testing of three lots of MP Diagnostics HTLV Blot 2.4 (using MP Biomedicals internal lot release panel as well as CBER lot release panel) were presented in the BLA. Lot release data demonstrated that the performance of MP Diagnostics HTLV Blot 2.4 in manual mode and semiautomated mode using MP Diagnostics AutoBlot System 20 is equivalent.

Effect of Anti-Coagulants

The effects of anti-coagulants on the performance of MP Diagnostics HTLV Blot 2.4 was evaluated using matched sets consisting of seven (7) types of anti-coagulant plasma (ACD, CPD, Sodium Citrate, K-Oxalate, K2 EDTA, Sodium Heparin, and PPT) and a serum specimen for reference. Each sample was tested both unspiked and spiked with a positive HTLV-I or HTLV-II specimen as compared to the reference sample. The presence or type of anticoagulant did not impact the performance of the HTLV Blot 2.4 in either spiked or unspiked samples.

C. Sensitivity

The sensitivity of the MP Diagnostics HTLV Blot 2.4 was evaluated in clinical studies on 200 repository plasma specimens obtained from blood donors with RR results on a licensed HTLV screening test that had been confirmed as Positive when fresh specimens were further tested with the CDPHL Algorithm. Testing of these specimens with the MP Diagnostics HTLV Blot 2.4 was performed at three geographically distinct clinical testing sites and compared with results of retesting by the CDPHL Algorithm. The summary results from testing this known positive population are shown in Table 4.

Table 4: MP Diagnostics HTLV Blot 2.4 and CDPHL Algorithm Results for Known Anti-HTLV Positive Specimens

		CDPHL Algorithm				
		HTLV-I POS	HTLV-II POS	IND	NEG	Total
MP Diagnostics HTLV Blot 2.4	HTLV-I POS	79	1	1	0	81
	HTLV-II POS	0	100	0	4	104
	HTLV-I/II POS, Undifferen-tiated	9	1	0	0	10
	IND	1	2	0	1	4
	NEG	0	0	0	1[a]	1
	Total	89	104	1	6	200

[a] One sample was negative by both the MP Diagnostics HTLV Blot 2.4 and the CDPHL Algorithm.

A greater number of known positive specimens were identified as Positive by the MP Diagnostics HTLV Blot 2.4 than by the CDPHL Algorithm [195 (81 HTLV-I Positive + 104 HTLV-II Positive + 10 HTLV-I/II Positive Undifferentiated) versus 193 (89 HTLV-I Positive + 104 HTLV-II Positive), respectively]. Of the 195 specimens identified as Positive by the HTLV Blot 2.4, 185 (81 + 104) were interpreted as HTLV-I Positive or HTLV-II Positive, and 10 (9 + 1) were HTLV-I/II Undifferentiated. Additionally, the HTLV Blot 2.4 identified more specimens as reactive (i.e., Positive or Indeterminate) than the CDPHL Algorithm (199 versus 194, respectively). Of the six specimens identified as Negative by the CDPHL Algorithm, four were identified as HTLV-II Positive by the MP Diagnostics HTLV Blot 2.4.

Although these 200 specimens were previously identified as Positive for HTLV antibodies using the CDPHL algorithm, six specimens were Negative and one was Indeterminate on retesting by the CDPHL Algorithm. This Indeterminate specimen was determined to be HTLV-I Positive by the MP Diagnostics HTLV Blot 2.4. One sample was negative by both the HTLV Blot 2.4 and the CDPHL Algorithm.

In this study, **the sensitivity of the MP Diagnostics HTLV Blot 2.4 was 97.5% [195 (81 + 104 + 10) / 200], with a 95% CI of 94.26% - 99.18%.** The Indeterminate rate for the HTLV Blot in this study was 2% (4/200). In comparison, the sensitivity of the CDPHL Algorithm was 96.5% (193/200), with a 95% CI of 92.92% - 98.58%, demonstrating no significant difference (p=0.48).

There were 10 specimens differentiated as HTLV-I (9) and HTLV-II (1) by the CDPHL Algorithm which were determined as HTLV-I/II Positive Undifferentiated by the HTLV Blot 2.4. These specimens all had IFA endpoint titers no greater than a two-fold difference. Of the remaining specimens, the HTLV Blot 2.4 was concordant for differentiation of HTLV-I in all 79 Positive cases, and was concordant for differentiation of HTLV-II in 100 out of 101 Positive cases. Overall, there were three cases in which the HTLV Blot 2.4 was Indeterminate. Based on these data, the MP Diagnostics HTLV Blot 2.4 reliably differentiated HTLV-I and HTLV-II Positive specimens.

D. Comparative Testing of RR Blood Donor Specimens Identified by Specific Licensed HTLV-I/II Screening Tests

Abbott PRISM HTLV-I/HTLV-II RR Specimens

A total of 200 specimens from blood donors that had previously tested repeatedly reactive using the Abbott PRISM HTLV-I/HTLV-II test were evaluated prospectively at three geographically distinct clinical testing sites using the MP Diagnostics HTLV Blot 2.4. Parallel results were obtained by the California Department of Public Health Laboratory using the CDPHL Algorithm. The results are shown in Table 5.

Table 5: MP Diagnostics HTLV Blot 2.4 and CDPHL Algorithm Results for Specimens that are RR using the Abbott PRISM HTLV-I/HTLV-II Screening Test

		CDPHL Algorithm			
		POS	*IND*	*NEG*	Total
MP Diagnostics HTLV Blot 2.4	*POS*	0	0	3[a]	3
	IND	0	0	109[b]	109
	NEG	0	3	85	88
	Total	0	3	197	200

[a] Two of these three specimens were confirmed to be true positives by follow-up testing of the donors. Follow-up testing was not obtained for the third donor.

[b] There were eleven specimens with p19 only and three with p24 only MP Diagnostics HTLV Blot 2.4 results.

Of these 200 specimens, the MP Diagnostics HTLV Blot 2.4 identified three as Positive, 109 as Indeterminate, and 88 as Negative. Comparatively, the CDPHL Algorithm identified three as Indeterminate and 197 as Negative. Follow-up testing that was available for one donor whose sample was Negative by the CDPHL Algorithm confirmed that the HTLV Blot 2.4 had correctly identified that specimen as Positive. Additionally, the three Indeterminate CDPHL Algorithm specimens that were identified as Negative by the HTLV Blot 2.4 were confirmed as Negative during donor follow-up; the CDPHL Algorithm result of Indeterminate was due to a falsely reactive WB that uses the less specific p21e recombinant. These results indicated a potentially higher sensitivity of the HTLV Blot 2.4 compared with the CDPHL algorithm, but a significantly higher rate of indeterminate results.

Avioq HTLV-I/II Microelisa System RR Specimens

A total of 105 preselected blood donor specimens with known results of testing by the CDPHL Algorithm that had previously tested repeatedly reactive using the Avioq HTLV-I/II Microelisa System (83 tested at ARC and 22 tested at Mississippi Valley Blood Center) were tested prospectively with the MP Diagnostics HTLV Blot 2.4 either at the MP Biomedicals, Solon, Ohio Laboratory (83) or at the California Department of Public Health Laboratory (22). The results are shown in Table 6.

Table 6: MP Diagnostics HTLV Blot 2.4 and CDPHL Algorithm Results for Specimens that are RR using the Avioq HTLV-I/II Microelisa System

		CDPHL Algorithm			
		POS	*IND*	*NEG*	Total
MP Diagnostics HTLV Blot 2.4	*POS*	50	0	0	50
	IND	0	0	18[a]	18
	NEG	0	4	33	37
	Total	50	4	51	105

[a] There were five specimens with p19 only and three with p24 only MP Diagnostics HTLV Blot 2.4 results.

Of these 105 specimens, the MP Diagnostics HTLV Blot 2.4 identified 50 as Positive, 18 as Indeterminate, and 37 as Negative. Comparatively, the CDPHL Algorithm identified 50 as Positive, four as Indeterminate, and 51 as Negative. The four CDPHL Algorithm Indeterminate results were due to the presence of p21e; all sample results were resolved as Negative by the MP Diagnostics HTLV Blot 2.4 due to the inclusion of GD21, a more specific envelope recombinant.

Fifty (50) specimens were concordantly identified as Positive by both the HTLV Blot 2.4 and the CDPHL Algorithm and 33 specimens were concordantly identified as negative. There were no false positive or false negative results of the HTLV Blot 2.4 compared with results on the CDPHL algorithm. These results indicated comparable sensitivity of the HTLV Blot 2.4 compared with the CDPHL algorithm, but a higher rate of indeterminate results with the HTLV Blot 2.4.

Table 7: Differentiation of positive specimens for those RR using the Avioq HTLV-I/II Microelisa System

		CDPHL HTLV Algorithm			
		HTLV-I	**HTLV-II**	**HTLV-I/II Undifferentiated**	***Total***
MP Diagnostics HTLV Blot 2.4	**HTLV-I**	13	0	5	*18*
	HTLV-II	0	27	2	*29*
	HTLV-I/II Undifferentiated	2	0	1	*3*
	Total	*15*	*27*	*8*	*50*

Among the 50 positive specimens, the HTLV Blot 2.4 identified 18 as HTLV-I and 29 as HTLV-II, and three specimens as HTLV-I/II Undifferentiated (see Table 7). In comparison, the CDPHL Algorithm identified 15 as HTLV-I, 29 as HTLV-II, and eight as HTLV-I/II Undifferentiated. These data indicated overall agreement between the HTLV Blot 2.4 and the CDPHL algorithm to differentiate HTLV-I and HTLV-II infections with concordant differentiation by the HTLV Blot 2.4 of 13/15 specimens categorized as HTLV-I by the CDPHL algorithm and 27/27 specimens categorized as HTLV-II by the CDPHL algorithm.

The combined results of the above summarized studies demonstrated that the MP Diagnostics HTLV Blot 2.4 is effective in resolving true positive and true negative status for specimens that are RR on either the Abbott PRISM HTLV-I/HTLV-II test or the Avioq HTLV-I/-II Microelisa System. False positive and false negative results were not seen with the MP Diagnostics HTLV Blot 2.4. However, high rates of Indeterminate results (109/197=55% for Abbott PRISM RR specimens and 18/51=35% for Avioq RR specimens) were obtained with specimens resolved as true negative by the CDPHL Algorithm. Some of these Indeterminate results were due to p19 only and p24 only HTLV blots which may be reclassified as Negative if additional studies of like specimens confirm that interpretation. Differentiation of HTLV-I and HTLV-II specimens also was accurate in comparison with the CDPHL algorithm.

VI. Bioresearch Monitoring (BIMO) Inspections

Inspections of the following clinical sites were conducted by BIMO investigators in accordance with FDA's Compliance Program Guidance Manual 7348.811:

Study Site	Location	Form FDA 483 Issued	Final Inspection Classification
LABS, Inc.	St. Louis, Missouri	Yes	VAI
American Red Cross Biomedical Services	Charlotte, North Carolina	Yes	VAI

Study Site	Location	Form FDA 483 Issued	Final Inspection Classification
California Department of Public Health Viral and Rickettsial Disease Laboratory	Richmond, California	No	NAI

VAI = Voluntary Action Indicated. NAI = No Action Indicated.

Bioresearch monitoring inspections of the three clinical study sites did not reveal significant problems that impact the data submitted in this BLA.

VII. Review Issues

The following issues were identified during the course of the review of this BLA:

1. *The MP Diagnostics HTLV Blot 2.4 with single gag protein bands (i.e., p19 only or p24 only) were initially interpreted as Negative. MP Biomedicals did not provide any data to support this interpretation.*

   Based on the discussions between FDA and the sponsor and discussions held at the November 2013 Blood Products Advisory Committee (BPAC) meeting, the sponsor agreed to a postmarketing commitment to perform additional testing on at least 25 blood donor specimens each that are repeatedly reactive on a donor screening assay and have an MP Diagnostics HTLV Blot 2.4 with p19 only, p24 only, or an *HGIP* pattern, that will include HTLV DNA PCR to determine the true infection status of these donors. In the meantime, MP Biomedicals will interpret the blots with p19 only or p24 only bands as Indeterminate.

2. *In the study of PRISM repeatedly reactive specimens (summarized in Table 5) there were originally eight specimens that were discordant (i.e., HTLV Blot Positive, CDPHL Algorithm Negative). MP Biomedicals had not provided any resolution testing for these specimens to determine the true infection status of the donor.*

   All eight donors of these discordant positive specimens were offered follow-up testing, and six were enrolled in the follow-up study. However, MP Biomedicals reviewed the data for these discordant results and determined that the clinical study site operator had misinterpreted five out of eight specimens. Two specimens were interpreted as Positive in the absence of a required rgp46-I band, and the strips for the other three specimens had a high background and were interpreted as Positive even though a clear banding pattern could not be determined. All five of these specimens should have been interpreted as Indeterminate rather than Positive. Of the three remaining donors with discordant results, for two donors whose follow-up testing was completed, the pivotal results were confirmed (i.e., these were true positive specimens).

3. *Although there are two FDA licensed HTLV-I/II screening tests currently available, in comparative testing of repeatedly reactive specimens with the MP Diagnostics HTLV Blot 2.4 and the CDPHL Algorithm, MP Biomedicals, had tested specimens that were repeatedly reactive using only one test (the Abbott PRISM HTLV-I/HTLV-II). There were no data to*

demonstrate that the HTLV Blot will perform similarly when used on specimens that are repeatedly reactive on the second licensed HTLV-I/II screening assay, the Avioq HTLV-I/II Microelisa System.

MP Biomedicals performed an additional study by testing 105 blood donor preselected specimens that were repeatedly reactive on the Avioq HTLV-I/II Microelisa System. Similar to the results with the Abbott PRISM HTLV-I/HTLV-II RR specimens, the HTLV Blot did not misclassify CDPHL categorized Positive or Negative specimens. However, the rate of Indeterminate HTLV Blot results among CDPHL-determined Negative specimens appeared to be somewhat lower with the Avioq HTLV-I/II Microelisa System.

VII. Blood Products Advisory Committee (BPAC) Meeting

The interpretive criteria of the MP Diagnostics HTLV Blot 2.4 were discussed at the BPAC meeting on November 1, 2013. In particular, FDA sought the advice of the Committee on whether it should consider reactivity limited to certain *gag* bands on the MP Diagnostics HTLV Blot 2.4 as a Negative result or an Indeterminate result.

The Committee agreed that there is sufficient evidence in the literature that individuals with *gag* protein bands without the p24 band (an "HTLV *gag* Indeterminate Pattern," or "*HGIP"*) are not infected and that blots with such patterns can be interpreted as Negative.

The Committee did not agree that there is sufficient evidence that individuals with a p19 only band or a p24 only band on the MP Diagnostics HTLV Blot 2.4 are not infected. The Committee recommended that blots with such patterns be interpreted as Indeterminate as opposed to Negative as proposed by MP Biomedicals. The Committee also suggested that MP Biomedicals perform additional studies that include HTLV DNA PCR on blood donor specimens with such HTLV blot banding patterns. The results of such a study could be used to modify the interpretative criteria of blots with p19-only or p24-only bands. MP Biomedicals intends to perform such a study as a Post Market Commitment.

VIII. Risk/Benefit Analysis

The MP Diagnostics HTLV Blot 2.4 is effective in correctly identifying HTLV-I/II Positive specimens and Negative specimens among those with RR results on licensed blood donor screening tests for antibodies to HTLV-I/II and reliably differentiates the antibodies as specific for HTLV-I and HTLV-II. These results will provide useful confirmatory information for donor counseling with regard to presence or absence of these infections. Additionally, as a single assay, the HTLV Blot 2.4 minimizes workload and turnaround time between testing and donor counseling compared with more complex algorithms. Availability of a licensed supplemental test for HTLV-I/II may enable FDA to consider development of a reentry algorithm for blood donors deferred on the basis of false positive screening tests for antibodies to HTLV-I/II. A limitation of the test is its high rate of indeterminacy on true negative specimens. This rate may be partially reduced if post-marketing studies support interpretation of blots with isolated p19 or p24 bands as Negative.

IX. Recommendations

a. Recommended Regulatory Action

Based on review of the information submitted in the BLA, responses to several information requests and a complete review letter, as well as a commitment from MP Biomedicals to perform additional post market studies, all review issues have been resolved. I recommend that this BLA be approved.

b. Recommendation for Post Market Activities

MP Biomedicals has agreed to a Post Market Commitment study that includes PCR testing on twenty-five (25) specimens each that are repeatedly reactive on an HTLV-I/II antibody screening test and have a banding pattern on the MP Diagnostics HTLV Blot 2.4 that is p24 only, p19 only, and *HGIP*. Based on these results the interpretive criteria for the MP Diagnostics HTLV Blot 2.4 may be revised.