WHO Prequalification of Diagnostics Programme
PUBLIC REPORT

Product: BD FACSPresto™ Near-Patient CD4 Counter System
PQ number: PQDx 0197-045-00

Abstract

BD FACSPresto™ Near-Patient CD4 Counter, BD CD4%CD4/Hb cartridge and BD FACSPresto™ cartridge kit with product codes, 651000, 657681 and 655495 manufactured by Becton, Dickinson and Company, CE-marked regulatory version, was accepted for the WHO list of prequalified in vitro diagnostics and was listed 19 September 2014

Intended use:
BD FACSPresto™ Near-Patient CD4 System consists of BD FACSPresto™ Counter and BD FACSPresto™ cartridge which contains dried flourochrome-conjugated antibody reagents. This automated system is intended for in vitro enumeration of CD4 absolute count, CD4 percentage and hemoglobin concentration in human capillary and venous blood specimens. The number of CD4+ T cells in the peripheral blood is currently used to decide when to initiate treatment and monitor response to treatment in HIV infected individuals.

Assay principle:
When blood is introduced into the BD FACSPresto™ cartridge, the specific antibodies bind to the surface antigens on the T lymphocytes and monocytes during the incubation period. When the stained cartridge is inserted into the counter, the dedicated software identifies and counts the CD4+ T lymphocyte absolute and percentage cells, and calculates the hemoglobin concentration. The BD FACSPresto™ cartridge also contains immobilized antibodies which the instrument uses to ensure that the reagents are present and sufficient blood specimen volume has been added.

The BD FACSPresto™ Near-Patient CD4 Counter System includes:

Catalogue Number	Product Description
651000	BD FACSPresto™ instrument packaging includes: • Portable instrument • Power supply • Adapter Cords • Instrument Cover • Work station • Printer Paper • USB Flash Drive • BD FACSPresto™ Power Supply Adapter

	• BD FACSPresto™ Near-Patient CD4 counter Instruction for use
657681	BD FACSPresto™ Cartridge packaging includes • BD FACSPresto™ Cartridge (100 tests) • BD™ Disposable (100 µL Pipettes) • BD FACSPresto™ Cartridge Instruction for use
655495	FACSPresto Cartridge Kit • BD FACSPresto™ Cartridge • BD FACSPresto™ finger stick sample collection kit • BD Microtainer Contact-Activated Lancet • Sterile Alcohol Prep Pads • Plastic Adhesive Bandage • A sterile Nonwoven Sponge
658210	• BD FACSPresto™ Instrument Carrying Case
658212	• BD FACSPresto™ Solar Charge Kit (includes solar panel, solar generator and power supply)
658885	• BD FACSPresto™ Solar Generator
658860	• BD FACSPresto™ Car Battery Charger Adapter (12V DC power adaptor)

Storage:
The BD FACSPresto™ cartridge should be stored at 4 °C to 31 °C.

Shelf-life:
12 months.

Summary of Prequalification status for BD FACSPresto™ Near-Patient CD4 Counter with BD CD4%CD4/Hb Cartridge and BD FACSPresto™ Cartridge kit

	Initial acceptance	
	Date	**Outcome**
Status on PQ list	18/09/2014	listed
Dossier assessment	28/08/2014	MR
Inspection status	13/08/2014	MR
Laboratory evaluation	25/08/2014	MR

MR: Meets Requirements

BD FACSPresto™ Near-Patient CD4 Counter System was accepted for the WHO list of in vitro prequalified diagnostics on the basis of data submitted and publicly available information.

Background information

Becton, Dickinson and Company submitted an application for prequalification of BD FACSPresto™ Near-Patient CD4 Counter System. Based on the established prioritization criteria, BD FACSPresto™ Near-Patient CD4 Counter System was given priority for prequalification.

Product dossier assessment

Becton, Dickinson and Company submitted a product dossier for BD FACSPresto™ Near-Patient CD4 Counter System as per the Instructions for compilation of a product dossier (PQDx_018 v1). The information submitted in the product dossier was reviewed by WHO staff and external experts (assessors) appointed by WHO in accordance with the internal report on the screening and assessment of a product dossier (PQDx_009 v2). Based on the product dossier screening and assessment findings, a recommendation was made to accept the product dossier for BD FACSPresto™ Near-Patient CD4 Counter System for prequalification.

Commitments for prequalification:
The manufacturer committed to amend and submit additional documentation on the following issues:

1. The current shelf life for the FACSPresto Cartridge is 12 months at 31 °C and is supported by accelerated stability studies. Real-time stability studies are on-going and expected to support the shelf life of 12 months at 31 °C. After conclusion of the study, the final stability report shall be written and submitted to the WHO by the

end of March 2015. In addition, BD shall submit a "Change Notification Form" to support any extension to the product shelf-life.

Manufacturing site inspection

A comprehensive inspection was performed at the site of manufacture (2350 Qume Drive, San Jose, 95131 CA, USA) of the BD FACSCount™ System in March 2011 as per the Information for manufacturers on prequalification inspection procedures for the sites of manufacture of diagnostics (PQDx_014 v1). The inspection found that the manufacturer had an acceptable quality management system and good manufacturing practices in place that ensured the consistent manufacture of a product of good quality. A quality management documentation review was performed in August 2014, and it was established that the manufacturer continuously implemented a quality management system in compliance with ISO 13485:2003 and that no significant changes were implemented since the first inspection.

Laboratory evaluation

The BD FACSPresto™ Near-Patient CD4 Counter System was evaluated in two WHO collaborating laboratories in Antwerp, Belgium and Dar es Salaam, Tanzania between May and July 2014. The evaluation was conducted using the WHO evaluation protocol (PQDx 114) which was also approved by in-country ethical review boards in Belgium and Tanzania. A total of 1630 fresh capillary and venous blood specimens in Tanzania and Belgium were used to study failure rates, reproducibility (intra-assay variation, inter assay variation, inter-instrument variation, instrument precision) and agreement with the FACSCalibur™ as the reference method. Lastly, ease to use was assessed.

The acceptance criteria are as follows: Specimen failure should be less than 10%. For reproducibility studies, a percentage coefficient of variation (%CV) should be less than 15% for CD4+ T counts of less than or equal to 200/µL and %CV should be less than 10% for CD4 counts of more than 200 cells/µL. Compared to the reference method, the bias should be less than 10%.

Specimen failure which was defined as failure of the instrument to provide valid results was between 0-9 % for venous whole blood and between 2.5 and 5.5% for capillary whole blood.

Testing of fresh specimens was conducted to assess the ability of the BD FACSPresto™ Near-Patient CD4 Counter System to provide reproducible results. The results indicated the following: the intra-assay variation on venous blood ranged from 4.7% to 7.0% for CD4 absolute counts and from 4.3% to 8% for CD4 percentages. The inter-instrument variability was below 4.8% for both CD4 absolute counts and CD4 percentages. The inter-assay variation for specimens kept up to 24 hours after collection ranged from 5.2% to 8% for CD4 absolute counts and CD4 percentages. Lastly, BD FACSPresto™ Near-Patient CD4

Counter System had precision of less than 4% for CD4 absolute counts in both venous and capillary whole blood.

Regarding agreement with the reference method and agreement between capillary and venous whole blood specimens, the correlation coefficients were high with minimal bias in both laboratories. The performance of BD FACSPresto™ Near-Patient CD4 Counter System to measure hemoglobin was not assessed in the current evaluation.

Operational characteristics of the BD FACSPresto™ Near-Patient CD4 Counter System were assessed using a structured questionnaire by testing personnel. The BD FACSPresto™ Near-Patient CD4 Counter System was found to be simple to use.

In conclusion, based on the results of evaluations conducted in two laboratories under the instruction of WHO, the performance of the BD FACSPresto™ Near-Patient CD4 Counter System fulfilled the WHO laboratory performance criteria using both venous and capillary whole blood specimens compared to BD FACSCalibur™.

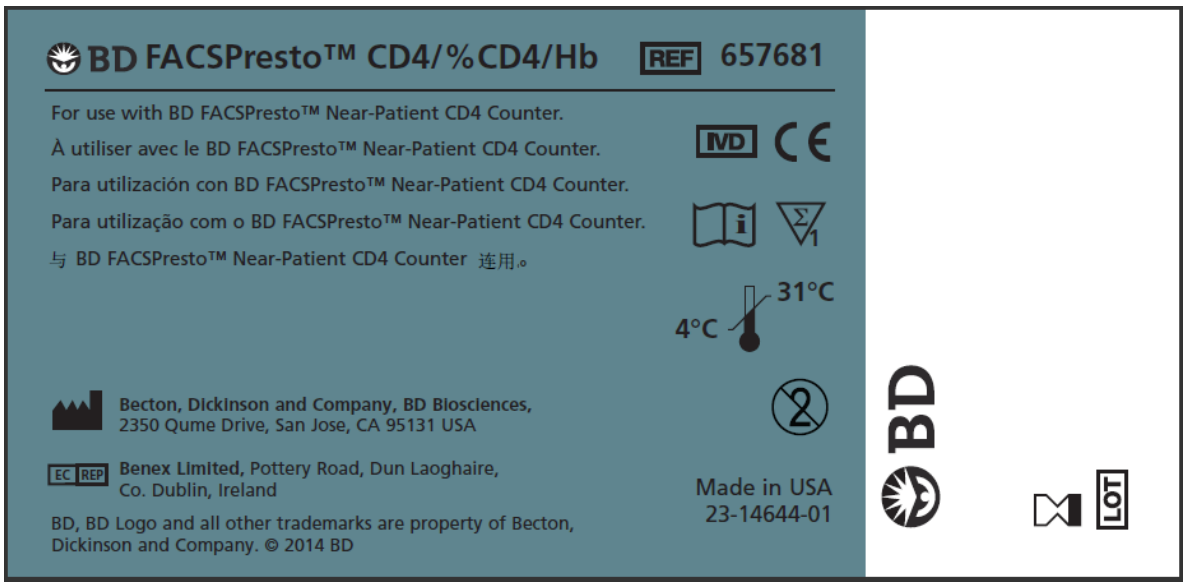
Labelling

1. Labels

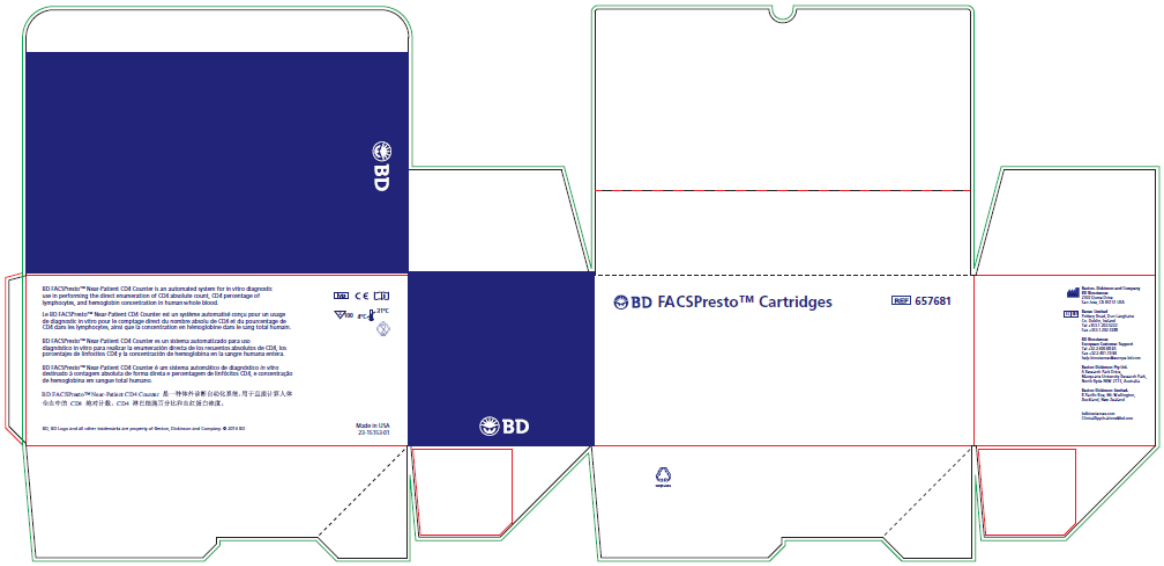
2. Instructions for use

1. Labels

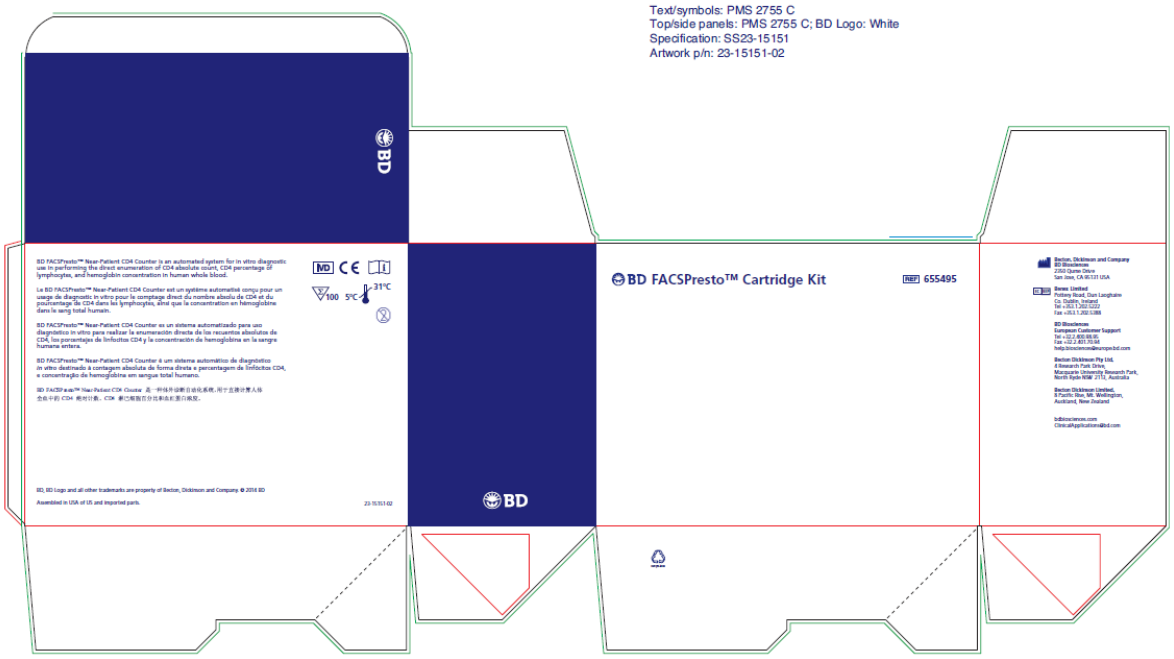
A. Cartridge Pouch Label



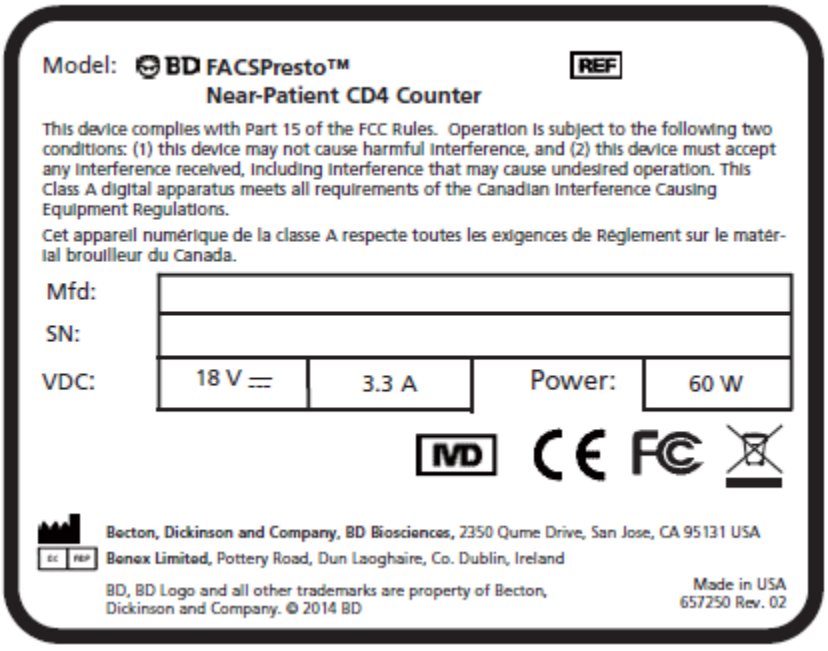
B. Cartridge Box Label



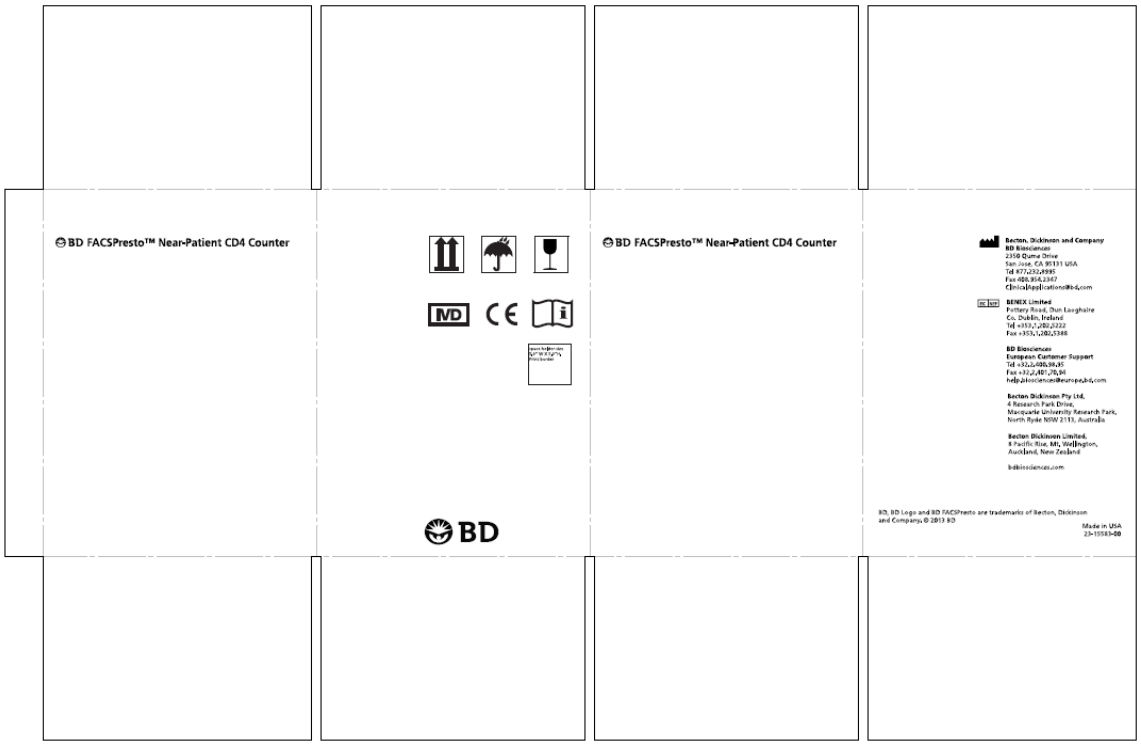
C. Cartridge Kit Box Label



D. Instrument Model Plate Label



E. Instrument Shipping box Label



2. BD FACSPresto Cartridge Instructions For Use

BD

BD FACSPresto™ Cartridge

100 Tests—Catalog No. 657681

3/2014 23-12814-00

IVD CE

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1. INTENDED USE

For use only with the BD FACSPresto™ Near-Patient CD4 Counter.

The BD FACSPresto Near-Patient CD4 Counter is an automated system for in vitro diagnostic use in performing the direct enumeration of CD4 absolute count, CD4 percentage of lymphocytes, and hemoglobin concentration in human whole blood.

Clinical Applications

CD4 counts and CD4 percentages (%CD4) have been used to evaluate the immune status of patients diagnosed with, or suspected of developing, immune deficiencies such as acquired immune deficiency syndrome (AIDS).[1,2]

The CD4 antigen is the receptor for the human immunodeficiency virus (HIV).[3] The absolute number and percentage of CD4 T lymphocytes are the cellular parameters most closely associated with HIV disease progression and patient prognosis.[4] The number of CD4 T lymphocytes declines in HIV infection.[5-7]

Hemoglobin is a protein in red blood cells that carries oxygen from the lungs to the body. Low or declining hemoglobin concentration is an indicator of anemia, a hematological abnormality frequently associated with HIV.[8-10]

2. PRINCIPLES OF THE PROCEDURE

The BD FACSPresto™ cartridge*, the CD4/%CD4/Hb cartridge, contains dried fluorochrome-conjugated antibody reagents. When blood reacts with the reagents, the antibodies in the reagents bind to the surface antigens on the

* BD FACSPresto Cartridge: US Patent 8,248,597

lymphocytes and monocytes. After the incubation period, the cells are analyzed on the BD FACSPresto Near-Patient CD4 Counter (the instrument). The software identifies the cell populations of interest and calculates CD4 absolute counts, CD4 percentages of lymphocytes, and hemoglobin concentration. The system measures total hemoglobin by a spectrophotometric method, using absorbance at an isobestic point for oxy-hemoglobin and deoxy-hemoglobin, with correction for scatter.

3. REAGENT COMPOSITION

The cartridge contains CD4 PE-Cy™5†/ CD3 APC/CD45RA APC/CD14 PE dried antibody reagents. The dried antibody reagents include inert ingredients such as buffer, bovine serum albumin (BSA), and ProClin®‡ as a preservative. CD3 APC and CD45RA APC enumerate total lymphocytes. Lymphocytes labeled with CD4 PE-Cy5 are designated $CD4^+$ lymphocytes. CD14 PE identifies monocytes, which are excluded from the analysis.

The CD4 antigen[11,12] (55 kDa)[13] is present on the helper/inducer T-lymphocyte subset[14,15] $CD3^+CD4^+$, which consists of 28% to 58%[16] of lymphocytes in normal peripheral blood,[12] and is present in low density on the surface and in the cytoplasm of monocytes. The CD4 antibody, clone SK3,[11] is derived from the hybridization of mouse myeloma cells with spleen cells from BALB/c mice immunized with human peripheral blood T lymphocytes. The CD4 antibody is composed of mouse IgG_1 heavy chains and kappa light chains.

The CD3 antibody, clone SK7, is derived from the hybridization of NS-1 mouse myeloma cells with spleen cells from BALB/c mice immunized with human thymocytes. CD3 is composed of mouse IgG_1 heavy chains and kappa light chains.

The CD45RA antigen is present on approximately 50% of $CD4^+$ T lymphocytes, approximately 75% of $CD8^+$ T lymphocytes, and on essentially all B lymphocytes and natural killer (NK) lymphocytes.[17] The helper/inducer T-lymphocyte subset expresses the phenotype $CD4^+CD45RA^+$.[17] The CD45RA antigen is expressed on naive T lymphocytes. Antigen density decreases upon in vitro activation.[18] A selective loss of the $CD4^+CD45RA^+$ subset during active multiple sclerosis has been demonstrated.[17,19]

The CD45RA antibody, clone HI100,[20] is derived from the hybridization of mouse myeloma cells with spleen cells isolated from mice immunized with human whole blood cells (WBCs).

The CD14 antigen is present on the majority of normal peripheral blood monocytes.[21] The CD14 antibody recognizes a human monocyte/ macrophage antigen of 55 kDa.[22] The CD14 antibody, clone MϕP9, is derived from the hybridization of Sp2/0 mouse myeloma cells with spleen cells from BALB/c mice immunized with peripheral

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‡ ProClin is a registered trademark of Rohm and Haas Company.

blood monocytes from a patient with rheumatoid arthritis. The CD14 antibody is composed of mouse IgG_{2b} heavy chains and kappa light chains.

4. PACKAGE CONTENTS

Each box contains 100 cartridges and 100 pipets.

5. STORAGE AND HANDLING

Store the cartridge:

- In its original foil pouch. Do not use the cartridge if the pouch has been opened for more than 30 minutes.
- At 4°C–31°C (39°F–88°F).
- In 10%–95% non-condensing humidity.
- Until the expiration date. Do not use the cartridge after the expiration date on the package.

Incubate the cartridge at 10°C–40°C (50°F–104°F).

6. MATERIALS REQUIRED BUT NOT PROVIDED

- BD FACSPresto™ instrument
- BD FACSPresto™ work station
- BD FACSPresto™ finger stick sample collection kit
- BD Vacutainer® EDTA blood collection tubes

7. CARTRIDGE QC

Cartridge Quality Control (QC) uses immobilized antibodies. The instrument verifies that the reagent is present and that there is sufficient sample in the cartridge. Cartridge QC runs automatically at every cartridge run.

8. PATIENT SPECIMENS

The assay is designed to be used only with peripheral whole blood collected by venipuncture into EDTA tubes or by finger stick.

Capillary[23] or venous blood samples are transferred directly into the cartridge and incubated. Samples are run on the instrument after incubation.

Follow these guidelines for handling your samples:

- Do not dilute whole blood before adding it to the cartridge.
- Do not refrigerate the whole blood specimen before sample preparation.
- Store whole blood collected in EDTA tubes at 20°C–25°C (68°F–77°F) up to 24 hours before applying the blood to the cartridge.
- Minimize exposure of the cartridges to light.
- Do not remove the channel protector on the cartridge until just before you insert the cartridge into the instrument.

WARNING Do not use previously fixed and stored samples. Whole blood specimens refrigerated before staining can give incorrect results. Specimens from patients taking immunosuppressive drugs can yield poor resolution.[24] Do not test hemolyzed specimens.

WARNING The reagents contain antibodies of mouse and rat origin.

WARNING All biological specimens and materials coming in contact with them are considered biohazards. Handle as if capable of transmitting infection[25,26] and dispose of with proper precautions in accordance with federal, state, and local regulations. Never pipette by mouth.

Wear suitable protective clothing, eyewear, and gloves.

WARNING Each cartridge is for single use only. Use one cartridge per specimen.

9. PROCESS CONTROLS

For information about process controls or external quality assessment products, contact your local BD Biosciences office or representative.

10. PROCEDURE

See the following for instructions on preparing and running samples.

- *BD FACSPresto Near-Patient CD4 Counter Instructions for Use* (IFU)
- *BD FACSPresto Near-Patient CD4 Counter Quick Reference Guide*

11. REFERENCE INTERVALS

The reference intervals for the BD FACSPresto cartridge shown in Table 1 are representative for hematologically normal adults.

Table 1 Representative reference intervals

Subset	Gender	N	Mean	Reference interval
CD4[27]	Male	77	811	462–1,306 cells/µL
	Female	83	866	440–1,602 cells/µL
%CD4[27]	Male	77	41	29%–54%
	Female	83	44	32%–55%
Hb[28]	Male	NA	NA	13.5–18.0 g/dL
	Female	NA	NA	12.0–16.0 g/dL

We recommend that laboratories and other users establish their own reference intervals for their patient populations using the BD FACSPresto system to reflect potential sources of variability, such as patient gender, race, age, and preparation techniques.

12. EXPECTED RESULTS

Performance of the BD FACSPresto cartridge (the cartridge) was established by the testing at the BD Biosciences laboratories in San Jose, CA, USA and at one clinical laboratory in Kisumu, Kenya, Africa.

Method Comparison

Absolute counts of CD4-positive cells, the percentage of CD4 positive cells in the lymphocyte population, and total hemoglobin concentration in whole blood from HIV-infected patients were determined using the BD FACSPresto system. Results were compared with results from the BD Tritest™ CD3 FITC/CD4 PE/CD45 PerCP reagent, in BD Trucount™ tubes, on the BD FACSCalibur™ flow cytometer, with the BD FACS™ Loader, using BD Multiset™ software and the Sysmex®§ KX-21 hematology analyzer. Whole blood samples were collected at the clinical laboratories. Regression statistics reported in Table 2 and Table 3 indicate the results are substantially equivalent. Details are shown in Figure 1 through Figure 5.

Table 2 Method comparison for venous blood

Parameter	N	R^2	Slope	Intercept	Range
CD4	189	0.98	0.97	7.37	55–2,478 cells/µL
%CD4	188	0.96	1.03	0.13	5.06%–53.77%
Hb	190	0.96	0.94	0.18	3–18.9 g/dL

§ Sysmex is a registered trademark of Sysmex America Inc.

Table 3 Method comparison for capillary blood

Parameter	N	R^2	Slope	Intercept	Range
CD4	162	0.97	1.03	13.47	69–2,474 cells/µL
%CD4	161	0.96	1.02	-0.26	5.9%–56.2%

Regression analysis is not applicable for hemoglobin capillary samples. A total of 163 samples were collected with a range of 4.7–17.1 g/dL. The average bias around the medical decision level (9.5 g/dL–11.5 g/dL) for capillary hemoglobin specimens was calculated against Sysmex as 2.02%.

Figure 1 Scatter plot with weighted Deming fit (y = 0.97x + 7.37) for venous blood (CD4)

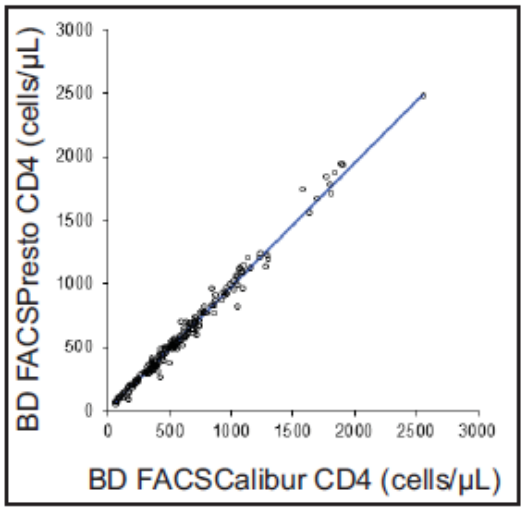


Figure 2 Scatter plot with Deming fit (y = 1.03x + 0.13) for venous blood (%CD4)

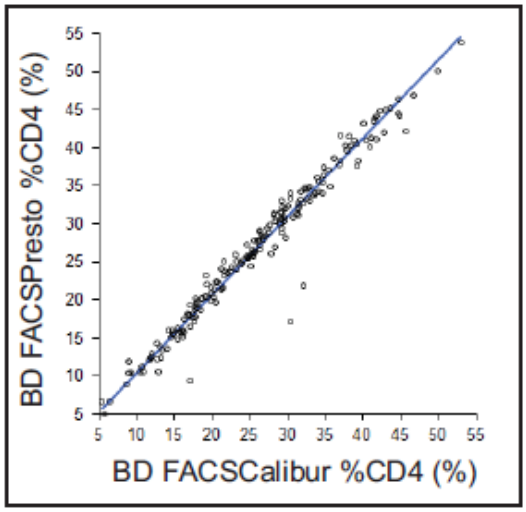


Figure 3 Scatter plot with weighted Deming fit (y = 1.03x + 13.47) for capillary blood (CD4)

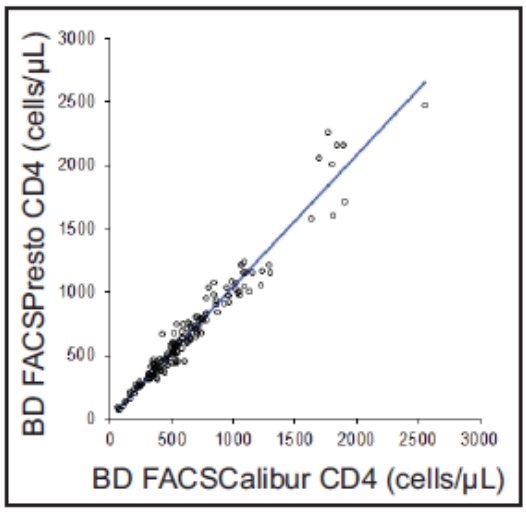


Figure 4 Scatter plot with Deming fit (y = 1.02x - 0.26) for capillary blood (%CD4)

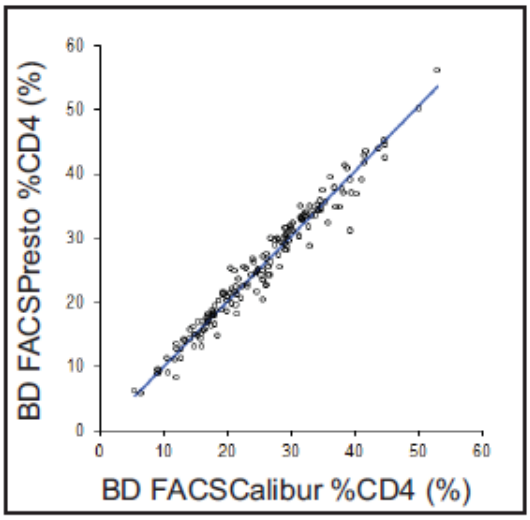
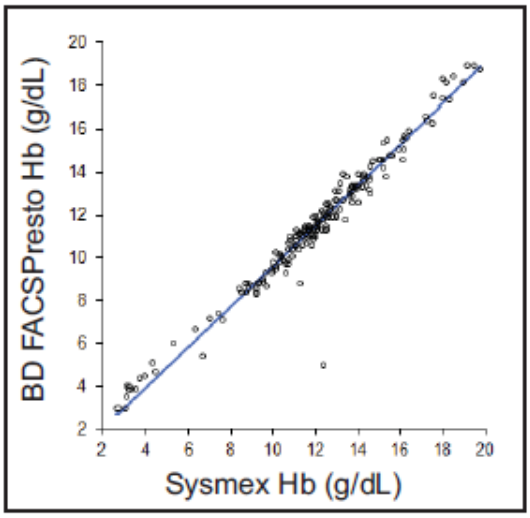


Figure 5 Scatter plot with Deming fit (y = 0.94x + 0.18) for venous blood (Hb)



Within-Specimen Reproducibility and Precision

Twenty replicates were created by one operator in one day, using two concentration levels of process controls, one lot of cartridges, and one instrument. Results are shown in Table 4.

Estimates of precision were determined at one site, BD Biosciences, using CD4 cellular and hemoglobin process controls. Two replicates of each CD4 control (normal and low) and two replicates of each of the 3 levels of hemoglobin controls were analyzed in each run, and two runs were performed per day for a total of 21 days. Three different instruments and three cartridge lots with three different operators were used, each for seven of the 21 days. Coefficients of variation (CVs) and standard deviations (SDs) are provided for CD4 absolute counts and CD4 percentages for within-run precision and total precision in Table 5 through Table 7, respectively.

Table 4 Repeatability study

	Level	Mean	CV	SD[a]	N
CD4	Low	155.10	5.78		20
	Normal	926.60	2.59		20
%CD4	Low	12.77		0.73	20
	Normal	43.99	1.53		20
Hb	Low	6.95	2.26		20
	Normal	12.99	1.09		20

a. Standard deviations (SDs) are reported instead of coefficients of variation (CVs) for %CD4 low level.

Table 5 Within-run and within-device precision CD4 absolute counts

	Low control (CV)	Normal control (CV)
Within-run	6.79	2.18
Within-device	6.79	3.30

Table 6 Within-run and within-device precision CD4 percentages

	Low control (SD[a])	Normal control (CV)
Within-run	0.75	1.58
Within-device	0.75	1.74

a. Standard deviations (SDs) are reported instead of coefficients of variation (CVs) for %CD4 low level.

Table 7 Within-run and within-device precision hemoglobin

	Low control (CV)	Medium control (CV)	High control (CV)
Within-run	2.42	1.46	1.07
Within-device	2.42	1.52	1.14

Stability

A stability study was conducted at the clinical laboratory in Kisumu to assess the following:

- Changes associated with the storage of whole blood before addition into the cartridge
- Changes as a result of time between addition of blood into the cartridge and data acquisition
- The combined effect of both

Whole blood samples were tested up to 24 hours post draw, and samples were tested up to 2 hours post addition of blood into the cartridge. All samples were maintained at room temperature (20°C–25°C, 68°F–77°F) before addition of blood into the cartridge or acquisition. Based on the results of this study, cartridges should be prepared with whole blood samples within 24 hours of draw, and then run within 2 hours of adding blood into the cartridge.

Linearity

Linearity was assessed in triplicate measurements of multiple concentrations of $CD4^+$ cells, lymphocyte cells, and hemoglobin across the reportable range of the assay for CD4 absolute counts, total lymphocytes, and hemoglobin on the instrument. Results are linear in the CD4 range (50–4,000 cells/µL), absolute lymphocyte range (200–10,000 cells/µL), and hemoglobin range (2–20 g/dL).

13. CARTRIDGE SPECIFICATIONS

Item	Description
Blood stability	Up to 24 hours after draw if stored in an EDTA tube at 20°C–25°C (68°F–77°F)
Sample stability	Up to 2 hours after addition of sample to cartridge
Sample throughput	More than 10 patient results per hour when run in batch mode
Validated range	CD4 count: 50–4,000 cells/µL %CD4: 5%–60% Hb concentration: 2.0–20 g/dL

14. LIMITATIONS

- Use the cartridge only with the BD FACSPresto instrument.
- The cartridge has no user-serviceable parts.
- Performance characteristics outside the validated range have not been established.
- Interfering substances in the sample may result in an inaccurate result.
- Follow the instructions in the IFU on preparing capillary and venous blood samples to ensure accurate results.

15. INTERFERING CONDITIONS

Table 8 lists the substances that were tested for interference with the reagents in the cartridge. Testing for interference was performed in accordance with EP7[29]. There was no detectable interference at the following concentrations.

Table 8 Interfering substances

Analyte	Max concentration
Acetaminophen	11.5 mg/dL
Ascorbic acid	6 mg/dL
Conjugated bilirubin	5 mg/dL
Creatinine	5 mg/dL
Hemolysis	20%
Methemoglobin	14%
Ibuprofen	28.5 mg/dL
Thrombocytes	3,805 x 10^9
Lipemia (intralipid)	2,400 mg/L
Salicylic acid	20 mg/dL
Tetracycline	10 mg/dL
Urea	40 mg/dL
Uric acid	3 mg/dL
Glucose	120 mg/dL
Albumin	5 g/dL
Iron	150 µg/dL
Magnesium	6.3 µg/dL
Isoniazid	40 µg/mL
Rifampicin	32 µg/mL
Ethambutol	12 µg/mL
Artesunate	150 ng/mL
Amodiaquine	15 ng/mL
Quinine	16 µg/mL
Zidovudine	1,000 ng/mL
Nevirapine	7 µg/mL

Table 8 Interfering substances

Analyte	Max concentration
Efavirenz	8 µg/mL
Tenofovir	1,000 ng/mL

WARRANTY

Unless otherwise indicated in any applicable BD general conditions of sale for non-US customers, the following warranty applies to the purchase of these products.

THE PRODUCTS SOLD HEREUNDER ARE WARRANTED ONLY TO CONFORM TO THE QUANTITY AND CONTENTS STATED ON THE LABEL OR IN THE PRODUCT LABELING AT THE TIME OF DELIVERY TO THE CUSTOMER. BD DISCLAIMS HEREBY ALL OTHER WARRANTIES, EXPRESSED OR IMPLIED, INCLUDING WARRANTIES OF MERCHANTABILITY AND FITNESS FOR ANY PARTICULAR PURPOSE AND NONINFRINGEMENT. BD'S SOLE LIABILITY IS LIMITED TO EITHER REPLACEMENT OF THE PRODUCTS OR REFUND OF THE PURCHASE PRICE. BD IS NOT LIABLE FOR PROPERTY DAMAGE OR ANY INCIDENTAL OR CONSEQUENTIAL DAMAGES, INCLUDING PERSONAL INJURY, OR ECONOMIC LOSS, CAUSED BY THE PRODUCT.

TROUBLESHOOTING

See the troubleshooting section in the *BD FACSPresto Near-Patient CD4 Counter Instructions For Use.*

REFERENCES

1. Giorgi JV, Hultin LE. Lymphocyte subset alterations and immunophenotyping by flow cytometry in HIV disease. *Clinical Immunology Newsletter.* 1990;10:55-61.
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