

41/26/99

K990327



COULTER

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Coulter Electronics, S.A.
Caracas, Venezuela

Date: January 29, 1999

Title: Summary of Safety and Effectiveness Information for 510(k) Premarket Notification

Product: reticONE™ SYSTEM for EPICS® XL Flow Cytometry Systems

Company: Coulter Corporation
11800 SW 147 Avenue
Miami, FL 33196-2500

Contact: Dr. Marion S. Gaide (M/C: 31-B06)
Senior Regulatory Affairs Specialist
Premarket Regulatory Affairs

Telephone: 305-380-2594

Common or Usual or Classification Name: Reticulocyte Analysis System with Reagents and Software for Flow Cytometry

Product Classification: Product Code: GKZ; C.F.R. Section: 864.5220; Classification Panel: Hematology and Pathology Devices; Device Class: II

Intended Use: The reticONE™ SYSTEM for EPICS® XL™ Flow Cytometry Systems combines

a reagent kit consisting of a Coriphosphine-O dye and a Biological Calibrator, and software for automated analysis of reticulocytes in whole blood using EPICS® XL™ Flow Cytometry Systems with SYSTEM II™ Software. The system is intended "For In Vitro Diagnostic Use" and allows identification and enumeration of reticulocyte percentage and absolute count.

Substantial Equivalence: 510(k) Premarket Notification: K872166
Retic-COUNT™ (Thiazole Orange*) Reagent
510(k) Premarket Notification: K880636
Retic-COUNT™ Reticulocyte Enumeration Software

Product Differences: The reticONE™ SYSTEM and Retic-COUNT™ are essentially identical with respect to features and principles of operation. The intended use of the New System and the Predicate System is the same. Further, the New System and the Predicate System use the same, well-established, state-of-the-art technologies of cell staining with a fluorescent dye-containing reagent and flow cytometric analysis to measure reticulocytes in whole blood [NCCLS Document H44-A]. Also, each system is designed for use with specific reagents, instruments and dedicated software for a) automated instrument set-up, standardization and operation; b) sample gating and data acquisition; c) flow cytometric analysis; and d) results generation and display. Finally, both systems are *alternatives* to standard microscopy for reticulocyte enumeration [NCCLS H16-P].

Product Testing: Product testing to assess the performance of the reticONE™ SYSTEM is described below. Studies were designed in line with instructions for use given in the reticONE™ SYSTEM Guide, Package Inserts, Product Manuals, and performance specifications. Specimens were assayed with Retic-COUNT™ for comparison purposes. The results of product testing demonstrate that the retic-ONE™ SYSTEM meets all performance specifications and provides reticulocyte percentage and absolute count values comparable to those of Retic-COUNT™.

1. Stability Studies:

Three studies were carried out to demonstrate whole blood specimen and sample stability claims for the reticONE™ SYSTEM.

a. *Stored (Unstained) Whole Blood Specimens Held for 72 Hours at 2-8 °C:*

Normal whole blood specimens (n = 3) were collected by venipuncture into K₃EDTA and ten replicate samples prepared for each specimen for each of four time points: 0-hours; 24-hours; 48-hours; and 72-hours after collection. The 0-hours samples were stained and analyzed for reticulocyte percentage within 30 minutes of specimen collection using the reticONE™ SYSTEM and EPICS® XL-MCL™ flow cytometer. The remaining samples were stained and analyzed for reticulocyte percentage after either 24-hours; 48-hours; or 72-hours of storage at 2-8°C. All analyses were carried out at 20-25° using the procedures described in the reticONE™ SYSTEM Guide. The results were analyzed in terms of reticulocyte percentage and standard deviation (± 1 SD) for each donor.

b. *Stored (Unstained) Whole Blood Specimens Held for 6 Hours at 20-25 °C:*

Normal whole blood specimens (n = 10) were collected by venipuncture into K₃EDTA and ten replicate samples prepared for each specimen for each of two time points: 0-hours and 6-hours after collection. The 0-hours samples were stained and analyzed for reticulocyte percentage within 30 minutes of specimen collection using the reticONE™ SYSTEM and EPICS® XL-MCL™ flow cytometer. The remaining samples were stained and analyzed for reticulocyte percentage after 6-hours of storage at 20-25°C. All analyses were carried out at 20-25° using the procedures described in the reticONE™ SYSTEM. The results were analyzed in terms of reticulocyte percentage and standard deviation (± 1 SD) for each donor.

c. *Stored Prepared (Stained) Samples Held for 6 Hours at 20-25 °C:*

Normal whole blood specimens (n = 5) were collected by venipuncture into K₃EDTA and ten replicate samples prepared for each specimen. The samples (0-hours) were stained and analyzed for reticulocyte percentage within 30 minutes of specimen collection using the reticONE™ SYSTEM and EPICS® XL-MCL™ flow cytometer. These *same* stained samples were reanalyzed for reticulocyte percentage after 6-hours of storage at 20-25°C. All analyses were carried out at 20-25° using the procedures described in the reticONE™ SYSTEM Guide. The results were analyzed in terms of reticulocyte percentage and standard deviation (± 1 SD) for each donor.

The results for the three stability studies clearly demonstrated that the reticONE™ SYSTEM meets stability claims for both stored (unstained) whole blood specimens and prepared (stained) samples under the storage times and temperature conditions studied.

2. Carryover Study:

Carryover percent was evaluated on two EPICS® XL-MCL™ flow cytometers by the approved NCCLS procedure for high-to-low carryover testing in a reticulocyte flow cytometric analysis system [NCCLS Document H44-A]. The High Level and the Low Level of the Streck Laboratories, Inc® multiple-level Reticulocyte Control product, Retic-Chex, were used in place of a whole blood specimen with an elevated RBC count and a whole blood specimen with a low RBC count. A single sample was prepared for each Level and stained with the COULTER® reticONE™ Reagent Kit. The stained High Level samples were then analyzed for reticulocyte percentage in three successive runs (Runs: I₁, I₂, I₃) using the reticONE™ SYSTEM and EPICS® XL-MCL™ flow cytometer. The stained Low Level samples were next analyzed in the same manner (Runs: J₁, J₂, J₃). All sample staining and analyses were carried out at 20-25° using the procedures described in the reticONE™ SYSTEM Guide. Carryover percent was calculated using the following equation: Carryover Percent (%) = $[(J_1 - J_3 \times 100) \div (I_3 - J_3)]$. The results for the carryover study clearly demonstrated that the reticONE™ SYSTEM exhibits minimal carryover compared to the Flow Cytometer Specification.

3. **Linearity Study:**

Two (n = 2) whole blood specimens were collected by venipuncture into K₃EDTA and serially diluted (n = 10 data points: low, high and 8 serial dilutions in between) to achieve a defined range of 0.2% to 12.5% reticulocytes. A sample was prepared for each data point and stained with the COULTER® reticONE™ Reagent Kit. Three replicate measurements of reticulocyte percentage were then made for each stained sample using the reticONE™ SYSTEM and EPICS® XL-MCL™ flow cytometer. All sample staining and analyses were carried out at 20-25° using the procedures described in the reticONE™ SYSTEM Guide. The results were analyzed in terms of regression and correlation analyses for recovered versus expected reticulocyte percentage. The results for the linearity study clearly demonstrated linearity over the defined (reportable) range for the reticONE™ SYSTEM.

4. **Precision Study:**

Three studies were carried out to demonstrate the reproducibility of the reticONE™ SYSTEM.

a. *Within Run (Intralaboratory) Precision:*

Measurements were made on samples from single [normal or abnormal] whole blood specimens for each of five levels of reticulocyte percentage using one EPICS® XL-MCL™ flow cytometer. All measurements were made in replicates of ten determinations. Results were analyzed in terms of mean reticulocyte percentage, standard deviation (± 1 SD) and coefficient of variation (%CV).

b. *Interlaboratory Precision:*

Measurements were made on samples from a single [normal] whole blood specimen for one level of reticulocyte percentage on the same day by three laboratories using different EPICS® XL-MCL™ flow cytometers. All measurements were made in replicates of ten determinations. Results were analyzed in terms of mean reticulocyte percentage, standard deviation (± 1 SD) and coefficient of variation (%CV).

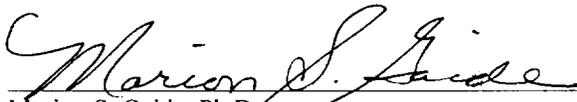
c. *Site Precision:*

Measurements were made on samples from single [normal or abnormal] whole blood specimens for each of five levels of reticulocyte percentage using one EPICS® XL-MCL™ flow cytometer. All measurements were made in replicates of ten determinations. Results were analyzed in terms of mean reticulocyte percentage, standard deviation (± 1 SD) and coefficient of variation (%CV).

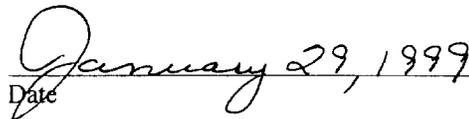
The results for the three precision studies clearly demonstrated the reproducibility of the reticONE™ SYSTEM.

5. **Accuracy Study:**

Normal and abnormal whole blood specimens were collected from geographically diverse populations of males and females unselected as to race and ranging in age from 18 to 85 years. Specimens were divided, processed and assayed in parallel with reticONE™ SYSTEM and Retic-COUNT™. Reticulocyte percentage (%) and absolute count (cells/ μ L) values were determined with EPICS® XL-MCL or FACScan™ flow cytometers (as applicable). Red blood cell counts were obtained using a COULTER® STKS™ Analyzer. The results were analyzed in terms of minimum, maximum, mean, standard deviation (± 1 SD), confidence intervals with 95% limits, regression and correlation analyses, and analyses of variance. The results for the accuracy study clearly demonstrated that the reticONE™ SYSTEM and Retic-COUNT™ identify and enumerate comparable numbers of reticulocytes in whole blood specimens.



Marion S. Gaide, Ph.D.
Senior Regulatory Affairs Specialist
Premarket Regulatory Affairs


Date



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Coulter Corporation
11800 SW 147 Avenue
Miami, Florida 33196-2500

APR 26 1999

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Re: K990327
Trade Name: reticONE™ SYSTEM for EPICS® XL™ Flow Cytometry Systems
Regulatory Class: II
Product Code: GKZ
Dated: January 29, 1999
Received: February 2, 1999

Dear Dr. Gaide:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

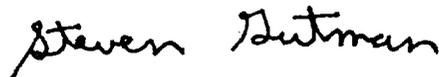
If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770) 488-7655.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597, or at its internet address "<http://www.fda.gov/cdrh/dsma/dsmamain.html>".

Sincerely yours,

A handwritten signature in black ink that reads "Steven Gutman". The signature is written in a cursive style with a large initial 'S'.

Steven I. Gutman, M.D, M.B.A.
Director
Division of Clinical
Laboratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

INDICATIONS FOR USE

K990327

510(k) Number (if known): ~~Not Yet Assigned~~

Device Name: reticONE™ SYSTEM for EPICS® XL™ Flow Cytometry Systems

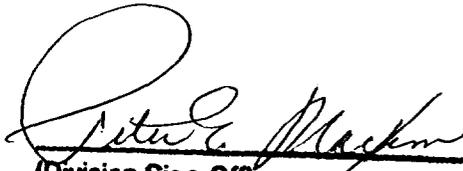
Indications For Use:

The reticONE™ SYSTEM for EPICS® XL™ Flow Cytometry Systems combines a reagent kit consisting of a Coriphosphine-O dye and a Biological Calibrator, and software for automated analysis of reticulocytes in whole blood using EPICS® XL™ Flow Cytometry Systems with SYSTEM II™ Software. The system is intended "For In Vitro Diagnostic Use" and allows identification and enumeration of reticulocyte percentage and absolute count.

The reticulocyte count is diagnostically useful in discriminating between normal and abnormal erythropoiesis. It can be useful in the diagnosis or detection of anemias, internal hemorrhaging, hemoglobinopathies and certain nutritional or vitamin deficiencies. Decreased or defective red cell production may result in a lower reticulocyte count such as in aplastic anemias. Elevated reticulocyte counts may be observed in clinical conditions where red cell destruction is increased (for example, hemolytic anemias and hypersplenism) or where there is increased red cell production (for example, erythropoietin drug therapy and a response to treated anemia).

Since the kidneys are a primary source of erythropoietin (a hormone that regulates erythroid development), the reticulocyte count is also affected in individuals with renal disease. In cases of renal atrophy, the reticulocyte count will be decreased. In cases of malignancy or hypersplenism, the reticulocyte count will be elevated.

Reticulocyte counts are also used as an indicator of bone marrow recovery following intensive cytotoxic chemotherapy or a bone marrow transplantation. Increased reticulocyte counts in these patients are indicative of bone marrow regeneration.


(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K990327

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use
(Per 21 CFR 801.109)

OR

Over-The-Counter Use _____