510(k) Summary APR - 3 1998

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K980819

A. Submitter:

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Contact: Sheila Ramerman
Date Prepared: March 27, 1998

B. Device Names:

Proprietary Name:	Biocircuits IOS® Free Thyroxine Test Cartridges Biocircuits IOS® Controls
Common names:	Reagents for free thyroxine measurement Quality control materials (assayed and unassayed)
Classification Name:	Free thyroxine test system Quality control materials (assayed and unassayed)

C. Legally Marketed Device:

The IOS Free Thyroxine Test Cartridges are substantially equivalent to the Dade Stratus Free Thyroxine Fluorometric Enzyme Immunoassay, currently manufactured and distributed by Dade International, Inc.

D. Device Description:

Free Thyroxine Test Cartridges:

Thyroxine (T4) is a small molecular weight hormone that is synthesized in the thyroid gland and secreted into the blood stream, and which plays an important role in regulating metabolism. The secreted hormone is reversibly bound to three plasma proteins in the serum: thyroxine binding globulin (TBG), thyroxine binding prealbumin (TBPA), and albumin (1). Greater than 99.5 % of thyroxine is bound by these plasma proteins, with 80% bound to TBG (2,3). The remaining T4 circulates as the free form in the serum. The free hormone is generally accepted to be the physiologically active hormone (4,5), and is believed to induce/control metabolism and to control thyroid hormone secretion by a feed-back loop through the thyroid gland, pituitary gland, and hypothalamus (8,9).

The bound T4 hormone fraction can be changed due to alterations or abnormalities in the properties of the binding proteins, or by malfunction of the thyroid gland. The free form of T4 remains at constant equilibrium compared to bound hormone, however, since it is not affected by variations in thyroxine binding proteins. The concentration of free T4, therefore, reflects thyroid function more closely than does the total T4 concentration (6,7).

Measurement of free T4 levels is useful when altered total T4 concentrations occur as a result of changes in T4 binding proteins, especially in TBG, and can differentiate true hyperthyroid and hypothyroid status from pseudo-hyperthyroxinemias and hypothyroxinemias in these cases (10). TBG levels remain relatively constant in healthy individuals, but normal pregnancy, steroid therapy, and oral contraceptive use can change the levels of TBG, changing the diagnosis from euthyroid to hypothyroid or hyperthyroid status (11,12, 13). In these conditions, the free T4 concentration remains constant while the total T4 level will fluctuate in parallel to TBG concentration changes. Free T4 levels have been reported to be altered due to treatment with drugs which can displace the bound T4, such as phenytoin, phenylbutazone, salicylates and diphenylhydantoin (14,15,16).

Principle of the Test

The IOS Free T4 assay is a sequential immunoassay in which free T4 in the patient serum sample first binds to a monoclonal anti-T4 antibody; this free T4:anti-T4 complex is then captured by polyclonal goat-anti-mouse immobilized on the plastic surface. Excess ('uncomplexed') anti-T4 antibody also binds to the surface. After an incubation period, any excess sample and unbound anti-T4 antibody are removed. In the second step, alkaline phosphatase-labeled T4 ('conjugate') is added, and the conjugate binds to T4 binding sites on the uncomplexed anti-T4 antibody. After another incubation period, excess conjugate is washed away and substrate is added. The substrate reacts with the conjugate bound to uncomplexed anti-T4 antibody and produces a fluorescent signal. The level of fluorescence is directly proportional to the amount of conjugate bound to the uncomplexed anti-T4 antibody and inversely proportional to the amount of free T4:T4 antibody complex, and thus inversely proportional to the amount of free T4 present in the serum sample. All the reagents necessary to perform the test are dried in the IOS Free T4 Test Cartridge, and are rehydrated by addition of patient sample by the operator or by the addition of buffer by the instrument.

To perform a test , the operator inserts an IOS Free T4 Test Cartridge into the IOS instrument. When prompted, the operator adds sample to the sample well and starts the test sequence. The instrument draws the cartridge inside and adds buffer to dilute the serum. The diluted serum rehydrates the dried reagent (mouse anti-T4 antibody) in the sample well. A short incubation period allows the serum and reagents to react. This mixture then flows into the incubation/ reaction chamber, where binding to the solid phase occurs. At the end of the incubation time, excess mixture is aspirated out of the incubation/reaction chamber by the instrument. Buffer is used to rehydrate conjugate in a separate chamber; rehydrated conjugate is allowed to enter the reaction chamber to bind to uncomplexed T4 antibody. At the end of this incubation time, excess conjugate is washed away by buffer dispensed by the instrument. Buffer is also used to rehydrate the substrate necessary for signal generation and quantitation in a third chamber;

rehydrated substrate is then allowed to enter the incubation/reaction chamber. The signal produced is read as a rate by front-surface fluorometry, compared to the signal produced by a series of calibrators stored in instrument memory, and the amount of free T4 present in the patient sample is calculated from the stored calibration curve.

IOS Controls: The use of materials derived from human blood to monitor quality control of clinical chemistry testing in the clinical laboratory has been widely established over the past several years. The Biocircuits IOS Controls are two levels of blood-based material for use with Biocircuits IOS Test Cartridges.

To run a control, the operator inserts the Control Cartridge (packaged with the controls) into the IOS instrument. The instrument reads the lot number and ranges of acceptable values for the control solutions from the Control Cartridge barcode, and then ejects the Control Cartridge. The operator then inserts a test cartridge and follows the instrument prompts to identify the control level, apply control solutions, and begin the test sequence. The IOS instrument performs the required buffer additions to rehydrate assay reagents and perform wash steps as necessary, reads the fluorescence signal generated, and calculates and prints the control result just as it would if the cartridge were used to test a patient sample.

E. Intended Use:

The IOS Free Thyroxine Test Cartridges are to be used for the quantitative determination of free thyroxine levels in serum for the diagnosis and treatment of thyroid diseases. They are intended to be used with the IOS instrument in clinical laboratories, physicians' office laboratories, and other alternate sites of use close to the point of patient care.

The IOS Controls are to be used to assist in monitoring accuracy and precision in the IOS immunoassay test cartridges.

F. Comparison with the Predicate Device:

Table I summarizes the comparative features of the IOS and Stratus assays.

G. Performance Data:

Free Thyroxine Test Cartridges:

Non-clinical testing performed in the manufacturer's laboratories gave the following results:

1. Precision:

Control Level	**1**	**2**	**3**
Mean (ng/dL)	1.21	3.59	0.56
SD, overall (ng/dL)	0.14	0.30	0.14
% CV, within-day (n=10)	11.3 %	8.2%	25.4%
% CV, between-day (n=40)	8.4%	13.1%	14.9%
% CV, total	13.12%	14.53%	28.08%

2. Accuracy:

A comparison of methods obtained by testing 119 patient samples in the manufacturer's laboratories using the IOS Free Thyroxine assay and a commercially available fluorescent enzyme immunoassay gave a correlation coefficient ('r') of 0.96, with the line of regression described by the equation y = -0.05 + 0.98x. Samples tested ranged from 0.2 to 4.6 ng/dL, and included pooled human serum spiked with T4 to obtain high concentrations of free T4.

Clinical testing performed in a typical physicians' office laboratory gave the following results:

1. Precision:

Control Level	**1**	**2**
number of replicates	44	40
Mean (ng/dL)	1.12	3.95
SD, overall (ng/dL)	0.14	0.56
% CV, total	12.58	14.22

2. Accuracy:

A comparison of methods was also performed by users in a typical physician's office laboratory. A total of 68 patient samples were tested using the IOS Free Thyroxine assay in the office laboratory; the samples were split and sent to the manufacturer's laboratory for testing by both the IOS and a commercially available fluorescent enzyme immunoassay. These studies gave a correlation with the commercially available assay of 0.962, with the line of regression described by the equation y = -0.14 + 1.10x. The samples tested ranged from 0.4 ng/dL to 4.9 ng/dL, and included pooled human serum spiked with T4 to obtain high concentrations of free T4.

IOS Controls:

The following ranges for the Free Thyroxine analyte in IOS Controls were determined in studies in the manufacturer's laboratories. To establish the ranges, each control level was tested in 80 cartridges, over at least 3 days, using several IOS instruments. These values only apply to this lot of IOS Controls. Different lots of IOS Controls will likely have slightly different ranges. Each laboratory should establish its own range for these controls over time.

	Control Level 1 lot # (to be assigned)	Control Level 2 lot # (to be assigned)
FT4 (ng/dL)	0.7 - 1.5	2.3 - 4.6

It is self-evident from the data and information presented here that the Biocircuits IOS Free Thyroxine Test Cartridges are as safe, effective, and perform as well as the Dade Stratus Free Thyroxine Fluorometric Immunoassay manufactured and distributed by Dade International, Inc.

Attachment: Table I: Assay Comparison

B-4

TABLE 1
Dade STRATUS vs. Biocircuits IOS®
Assay Comparison

ATTRIBUTE	STRATUS FT4	IOS FT4
Technology	Fluorometric enzyme immunoassay	Fluorometric enzyme immunoassay
Assay format	Sequential	Sequential
Enzyme label	Alkaline phosphatase	Alkaline phosphatase
Substrate	Methylumbelliferyl phosphate	Methylumbelliferyl phosphate
Reagents		
Immobilization Medium	Reaction tab	Plastic cartridge
Dry	Polyclonal anti-T4	Polyclonal anti-mouse, monoclonal anti-T4, T4-conjugate, substrate
Wet	3 (assay-specific), loaded by operator at start of each run	1 (diluent, used for all assays), continuously on board
Delivery	Fully automated	Fully automated
Calibration	User-generated	Factory-generated
Calibration Stability	14 days (minimum)	120 days (minimum)
Storage	Refrigerated (2-8°C)	Room Temperature (15-30°C)
Sample		
Type	Serum or plasma	Serum
Volume	0.2 ml (minimum)	0.033mL
Measurement Needed	Non-precision	Precision
Operating environment	22°-32° C	15°-30° C
Data analysis	Microprocessor-controlled Stored standard curves, user-generated	Microprocessor-controlled Stored standard curves, factory-generated
Data output	LCD display Printed alphanumeric hard copy	LCD display Printed alphanumeric hard copy

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

APR - 3 1998

Sheila J. Ramerman
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Biocircuits Corporation
1324 Chesapeake Terrace
Sunnyvale, California 94089

Re: K980819
Biocircuits IOS® (In-Office-System) Free Thyroxine (Free T4, FT4) Test Cartridges and IOS Controls
Regulatory Class: I & II
Product Code: JJY, CEC
Dated: March 2, 1998
Received: March 3, 1998

Dear Ms. Ramerman:

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 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/dsmamain.html".

Sincerely yours,

Steven Gutman

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

510(k) Number: K980819

Device Name: Biocircuits IOS® Free Thyroxine Test Cartridges and IOS Controls

Indications for Use:

The IOS Free Thyroxine Test Cartridges are intended to be used for the quantitative determination of free (not protein bound) thyroxine (thyroid hormone) in serum for the diagnosis and treatment of thyroid diseases. They are intended to be used with the Biocircuits IOS® instrument in clinical laboratories, physician office laboratories, and other alternate sites of use close to the point of patient care.

The IOS Controls are to be used to assist in monitoring accuracy and precision in the IOS immunoassay test cartridges.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K980819

Prescription Use ✓ OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

(Optional Format 1-2-96)